(1)

(19)日本国特許庁（ＪＰ）　(12) 特　許　公　報（Ｂ２）　(11)特許番号

第2893191号

(45)発行日　平成11年(1999) 5月17日　(24)登録日　平成11年(1999) 3月5日

(51)Int.Cl.⁶	識別記号	ＦＩ	
Ａ６１Ｋ　47/14		Ａ６１Ｋ　47/14	Ｃ
9/16		9/16	Ｕ
47/22		47/22	Ｄ
47/34		47/34	Ｃ

請求項の数14(全 15 頁)

(21)出願番号　特願平1－259674

(22)出願日　平成1年(1989)10月3日

(65)公開番号　特開平2－223533

(43)公開日　平成2年(1990) 9月5日

審査請求日　平成8年(1996) 9月25日

(31)優先権主張番号　特願昭63－282994

(32)優先日　昭63(1988)11月8日

(33)優先権主張国　日本（ＪＰ）

(31)優先権主張番号　特願昭63－294379

(32)優先日　昭63(1988)11月21日

(33)優先権主張国　日本（ＪＰ）

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(54)【発明の名称】　放出制御性マトリックス剤

(57)【特許請求の範囲】

【請求項１】ポリグリセリン脂肪酸エステルまたはそれを含有してなる常温で固体のマトリックスに薬効成分が分散しているマトリックス剤。

【請求項２】ポリグリセリン脂肪酸エステルまたはそれを含有してなる常温で固体のマトリックスに薬効成分が分散している細粒剤または顆粒剤。

【請求項３】マトリックスにマイクロクリスタリンワックスを含有してなる請求項（１）記載のマトリックス剤。

【請求項４】マトリックスにマイクロクリスタリンワックスを含有してなる請求項（２）記載の細粒剤または顆粒剤。

【請求項５】コーティングしてなる請求項（２）または（４）記載の細粒剤または顆粒剤。

【請求項６】請求項（２）または（５）記載の細粒剤または顆粒剤をカプセルに充填してなるカプセル剤。

【請求項７】請求項（２）または（５）記載の細粒剤または顆粒剤を打錠してなる錠剤。

【請求項８】崩壊剤を含有してなる請求項（７）記載の錠剤。

【請求項９】ポリグリセリン脂肪酸エステルまたはそれを含有してなる常温で固体のマトリックスに酸性薬効成分と水に不溶ないし難溶の固体塩基とが分散している細粒剤または顆粒剤。

【請求項１０】ポリグリセリン脂肪酸エステルまたはそれを含有してなる常温で固体のマトリックスに塩基性薬効成分と腸溶性物質とが分散している細粒剤または顆粒剤。

【請求項１１】コーティングしてなる請求項（９）また

は（10）記載の細粒剤または顆粒剤。

【請求項１２】請求項（９）、（10）または（11）記載の細粒剤または顆粒剤をカプセルに充填してなるカプセル剤。

【請求項１３】請求項（９）、（10）または（11）記載の細粒剤または顆粒剤を打錠してなる錠剤。

【請求項１４】崩壊剤を含有してなる請求項（13）記載の錠剤。

【発明の詳細な説明】

「産業上の利用分野」

本発明は安定な放出制御性マトリックス剤に関する。

「従来の技術」

放出制御性（controlled release）とりわけ持続性製剤は、効力を持続させて投与回数をへらす、また、血中濃度の急激な立ち上がりを押えて副作用を軽減する、血中濃度を長時間一定に保つ等の目的から種々の薬物、方法で検討がなされている。放出制御性製剤には、薬物を含む核の部分が膜によっておおわれたカプセルタイプ，放出制御層中に薬物が分散したマトリックスタイプなどがある。

これら従来の放出制御性製剤は、種々の製剤的工夫を施す必要があるため、錠剤、カプセル剤、あるいは顆粒剤の形をとっている。

「発明が解決しようとする課題」

しかしながら、近年服薬する患者が高齢者、子供なども多いことを考えると、細粒の放出制御性製剤が望まれる。また、服用量調整が容易なことも、細粒剤の利点の１つである。しかし、従来の放出制御性製剤に準じて製造したのでは、安定な放出制御性製剤特に細粒剤を得ることはできなかった。そのために今迄に商品化された放出制御性細粒剤はまだない。

「課題を解決するための手段」

そこで本発明者らは、製造法が容易かつ経済的で、人体に有害な溶媒を用いず、溶出速度の調整が容易で服用しやすく、しかも安定な放出制御性マトリックス剤につき種々検討した結果、従来のマトリックス剤では使用されたことのないポリグリセリン脂肪酸エステルまたはそれを含有してなる常温（15～35℃）で固体のマトリックスに薬効成分を分散させてマトリックス剤特に細粒剤または顆粒剤を製造すると、予想外にも安定性、放出制御性とりわけ持続性のみならず経済性、毒性、効果等において極めて優れた理想的な放出制御性マトリックス剤が得られること、さらに上記マトリックス剤の製造において酸性薬効成分と水に不溶ないし難溶の固体塩基とを分散させる、あるいは塩基性薬効成分と腸溶性物質とを分散させると、上記の優れた特性に加えてpH非依存性（胃及び腸において一定の速度で薬効成分が溶出する）の放出制御性細粒剤が得られること、得られたマトリックス剤をコーティングすることにより更に安定な放出制御性が得られること、得られたマトリックス剤が商品化に好適であることを見出し、これらに基づいて本発明を完成した。

即ち、本発明は、

（１）ポリグリセリン脂肪酸エステルまたはそれを含有してなる常温で固体のマトリックスに薬効成分が分散しているマトリックス剤、

（２）ポリグリセリン脂肪酸エステルまたはそれを含有してなる常温で固体のマトリックスに薬効成分が分散している細粒剤または顆粒剤、

（３）マトリックスにマイクロクリスタリンワックスを含有してなる第（１）項記載のマトリックス剤、

（４）マトリックスにマイクロクリスタリンワックスを含有してなる第（２）項記載の細粒剤または顆粒剤、

（５）コーティングしてなる第（２）または（４）項記載の細粒剤または顆粒剤、

（６）第（２）または（５）項記載の細粒剤または顆粒剤をカプセルに充填してなるカプセル剤、

（７）第（２）または（５）項記載の細粒剤または顆粒剤を打錠してなる錠剤、

（８）崩壊剤を含有してなる第（７）項記載の錠剤、

（９）ポリグリセリン脂肪酸エステルまたはそれを含有してなる常温で固体のマトリックスに酸性薬効成分と水に不溶ないし難溶の固体塩基とが分散している細粒剤または顆粒剤、

（10）ポリグリセリン脂肪酸エステルまたはそれを含有してなる常温で固体のマトリックスに塩基性薬効成分と腸溶性物質とが分散している細粒剤または顆粒剤、

（11）コーティングしてなる第（９）または（10）項記載の細粒剤または顆粒剤、

（12）第（９）、（10）または（11）項記載の細粒剤または顆粒剤をカプセルに充填してなるカプセル剤、

（13）第（９）、（10）または（11）項記載の細粒剤または顆粒剤を打錠してなる錠剤、

（14）崩壊剤を含有してなる第（13）項記載の錠剤、

本発明において用いられるポリグリセリン脂肪酸エステルは、ポリグリセリンと脂肪酸とのエステルである。ポリグリセリンは、「１分子中にｎ個（環状）～ｎ＋２個（直鎖・分枝状）の水酸基と、ｎ－１個（直鎖・分枝状）～ｎ個（環状）のエーテル結合をもった多価アルコール」であり［“ポリグリセリンエステル”阪本薬品工業株式会社編集，発行（1986年５月２日）第12頁］、たとえば式

$$HO\!\left(CH_2-\underset{\displaystyle OH}{\underset{|}{C}H}-CH_2-O\right)_n H \qquad [I]$$

［式中、ｎは重合度を示す。］で表わされるもの等が用いられ、ｎとしては通常２～50、好ましくは４～20の整

数が用いられる。この様なポリグリセリンの具体例としては、たとえばジグリセリン、トリグリセリン、テトラグリセリン、ペンタグリセリン、ヘキサグリセリン、ヘプタグリセリン、オクタグリセリン、ノナグリセリン、デカグリセリン、ペンタデカグリセリン、エイコサグリセリン、トリアコンタグリセリン等が用いられ、特にたとえばテトラグリセリン、ヘキサグリセリン、デカグリセリン等が繁用される。また、脂肪酸としては、たとえば炭素数８～40、好ましくは12～22の飽和または不飽和高級脂肪酸等を用いることができる。この様な脂肪酸としては、たとえばパルミチン酸、ステアリン酸、オレイン酸、リノール酸、リノレン酸、ミリスチン酸、ラウリン酸、リシノール酸、カプリル酸、カプリン酸、ベヘニン酸等が用いられ、とりわけたとえばステアリン酸、オレイン酸、ラウリン酸、リシノール酸等が繁用される。ポリグリセリン脂肪酸エステルは、上記のごときポリグリセリンと脂肪酸とのモノエステルまたはポリエステルが用いられる。この様なポリグリセリン脂肪酸エステルは、分子量が通常200～5000、好ましくは300～2000であり、HLB（hydrophile-lypophile balance;親水性親油性バランス）が通常１～22、好ましくは１～15のものが用いられる。また、ポリグリセリン脂肪酸エステルは、用いられる薬効成分により適宜選択することができ、たとえば薬効成分を0.00001～5g/ml、好ましくは0.0001～1g/ml加温溶融させることができるものを用いてもよい。ポリグリセリン脂肪酸エステルの具体例としては、たとえばカプリル酸ジ（トリ）グリセリド、カプリン酸ジ（トリ）グリセリド、カプリル酸モノ（デカ）グリセリド、ラウリン酸モノ（デカ）グリセリド、ラウリン酸モノ（ヘキサ）グリセリド、ラウリン酸モノ（テトラ）グリセリド、オレイン酸ジ（トリ）グリセリド、オレイン酸ジ（テトラ）グリセリド、リノール酸ジ（トリ）グリセリド、リノール酸ジ（テトラ）グリセリド、リノール酸ジ（ヘキサ）グリセリド、リノール酸（ヘプタ）グリセリド、ステアリン酸モノ（デカ）グリセリド、ステアリン酸デカ（デカ）グリセリド、ステアリン酸モノ（テトラ）グリセリド、ステアリン酸モノ（ヘキサ）グリセリド、ステアリン酸セスキ（ヘキサ）グリセリド、ステアリン酸トリ（ヘキサ）グリセリド、ステアリン酸ペンタ（ヘキサ）グリセリド、オレイン酸セスキ（デカ）グリセリド、オレイン酸ペンタ（ヘキサ）グリセリド、オレイン酸モノ（ヘキサ）グリセリド、オレイン酸モノ（デカ）グリセリド、オレイン酸デカ（デカ）グリセリド、ステアリン酸トリ（テトラ）グリセリド、ステアリン酸ペンタ（テトラ）グリセリド、オレイン酸モノ（テトラ）グリセリド、オレイン酸ペンタ（テトラ）グリセリド、パルミチン酸モノ（デカ）グリセリド、パルミチン酸デカ（デカ）グリセリド、パルミチン酸モノ（ヘキサ）グリセリド、パルミチン酸セスキ（ヘキサ）グリセリド、パルミチン酸トリ（ヘキサ）グリセリド、パルミチン酸ペンタ（ヘキサ）グリセリド、パルミチン酸モノ（テトラ）グリセリド、パルミチン酸トリ（テトラ）グリセリド、パルミチン酸ペンタ（テトラ）グレセリド等の１種または２種以上の混合物が用いられ、好ましくはたとえばステアリン酸ペンタ（テトラ）グリセリド（たとえば阪本薬品（株）製のPS-310等）、ステアリン酸モノ（テトラ）グリセリド（たとえば阪本薬品（株）製のMS-310等）、ステアリン酸ペンタ（ヘキサ）グリセリド（たとえば阪本薬品（株）製のPS-500等）、ステアリン酸セスキ（ヘキサ）グリセリド（たとえば阪本薬品（株）製のSS-500等）、ステアリン酸モノ（デカ）グリセリド等が繁用される。とくに、ポリグリセリン脂肪酸エステルがステアリン酸モノ（デカ）グリセリドである場合には薬効成分の吸収が良好でかつ安定な放出制御性が得られる。これらポリグリセリン脂肪酸エステルの使用量は、目的が達成される限り特に限定されないが、通常重量換算で薬効成分の約0.001～10000倍、好ましくは0.001～50倍、より好ましくは0.005～５倍である。

また、本発明においては、ポリグリセリン脂肪酸エステルを含有してなる常温で固体のマトリックスが用いられる。このマトリックスには、上記で述べたごときポリグリセリン脂肪酸エステルを上記の使用量含有させるのがよい。本発明におけるマトリックスは、常温で固体であって特に融点30～150℃好ましくは40～120℃のものが用いられる。このマトリックスには、ポリグリセリン脂肪酸エステルに加えてたとえば脂質等を含有させることにより一層好ましい結果を得ることができる。この様な脂質としては、製剤上許容しうる水不溶性物質であり医薬の溶出速度を調整する作用を有するものが用いられ、好ましくは軟化点または融点として40～120℃より好ましくは40～90℃を有する脂質が用いられる。脂質の具体例としては、たとえば硬化油（たとえばヒマシ油、綿実油、大豆油、菜種油、牛脂等）、蜜ロウ、カルナバロウ、鯨ロウ、レシチン，パラフィン、マイクロクリスタリンワックス、たとえばステアリン酸、パルミチン酸等の脂肪酸またはその塩（たとえばナトリウム塩、カリウム塩等）、たとえばステアリルアルコール、セチルアルコールなどの脂肪アルコール、グリセライドなどが用いられ、とりわけたとえば硬化綿実油、硬化ヒマシ油、硬化ダイズ油、カルナバロウ、ステアリン酸、ステアリルアルコール、マイクロクリスタリンワックス等が繁用される。脂質の使用量は、目的に支障の範囲で使用されることができ、通常重量換算で薬効成分の約0.01～100倍好ましくは１～20倍である。

本発明における常温で固体のマトリックスには、特に支障のない限り、一般にマトリックス剤特に細粒剤または顆粒剤の製造に用いられる添加剤を適宜使用することができる。例えば乳糖、コーンスターチ、アビセル、粉糖、ステアリン酸マグネシウム等の賦形剤、たとえばでんぷん、ショ糖、ゼラチン、アラビアゴム末、メチルセ

ルロース、カルボキシメチルセルロースナトリウム、ヒドロキシプロピルメチルセルロース、ポリビニルピロリドン等の結合剤、たとえばカルボキシメチルセルロースカルシウム、L-ヒドロキシプロピルセルロース等の崩壊剤、その他着色剤、矯味剤、吸着剤、防腐剤、湿潤剤、帯電防止剤、崩壊延長剤等を適宜添加できる。

薬効成分としては、比較的融点の高い（たとえば約121℃以上）医薬、たとえば塩酸フェニルプロパノールアミン、マレイン酸クロルフェニラミン、塩酸フェニレフリン、テオフィリン、カフェイン、塩酸プロカインアミド、スルファニルアミド、セファレキシン、アンピシリン、モルシドミン、インドメタシン、スルフィソキサゾール、スルファダイアジン、ディアゼパム、バルプロ酸、硫酸キニジン、アスピリン、3,4－ジヒドロ－2,8－ジイソプロピル－３－チオキソ－2H－1,4－ベンズオキサジン－４－アセティックアシッド（以下“AD-5467"と称する）、塩酸デラプリル、イプリフラボン、トレピブトン等や、比較的融点の低い（約０～120℃、好ましくはたとえば約40～120℃）医薬、たとえば硝酸イソソルバイド、ケトプロフェン、シクランデレート、イデベノン、２－（12－ヒドロキシドデカ－5,10－ジイニル）－3,5,6－トリメチル－1,4－ベンゾキノン（以下“AA-861"と称する）などが用いられるほか、たとえばインスリン、バソプレッシン、インターフェロン、IL-2、ウロキナーゼ、a.FGF、b.FGFなどのペプタイド、タンパク等も薬効成分として用いることができ、本発明のマトリックス剤ではこれら医薬を徐々に消化管中で溶解または（および）吸収させることができる。

これら薬効成分はその性質により消化管内における溶解性、吸収部位などが異なる。一般的に塩基性薬効成分は、酸性側では溶解性がますがアルカリ側では溶解性は低下するので、最初に通過する胃では酸性のため薬効成分の溶出ははやいが中性～弱アルカリ性の腸では溶出がおそい。また、酸性薬効成分は、アルカリ側では溶解性がますが酸性側では溶解性は低下するので、中性～弱アルカリ性の腸では溶出がはやいが最初に通過する胃では酸性のため溶出はおそい。そこで胃および腸の両方において一定の速度で薬効成分の溶出が行われるように、pHとは無関係にてきせつな溶出を保持するため、本発明においては、ポリグリセリン脂肪酸エステルまたはそれを含有してなる常温で固体のマトリックスに、酸性薬効成分と水に不溶ないし難溶の固体塩基とを分散させる、あるいは塩基性薬効成分と腸溶性物質とを分散させることを行ってもよい。

ここにおいて、酸性薬効成分は水溶液が酸性（たとえばpH1.5以上ないし7.0未満、好ましくは2.0～6.8）を示すものあるいは酸性基（たとえばカルボキシル基等）を有するものであり、たとえばインドメタシン、サリチル酸、AD-5467、トレピブトン、アモキサノクス、アスピリン、バルプロ酸、ケトプロフェン、イブプロフェン、エピネフリン、ハロペリドール、レセルピン、アスコルビン酸、アセトアミノフェン、プロベネシド等が用いられ、特にAD-5467、トレピブトン、インドメタシン等が繁用される。固体塩基は、水に不溶ないし難溶（水に対する溶解度は37℃で0.1g/ml以下好ましくは0.001g/ml以下）のものが用いられるが、溶解度の低いほうが好ましい結果が得られる。この様な固体塩基としては、たとえば酸化マグネシウム，水酸化マグネシウム，ケイ酸マグネシウム，炭酸マグネシウム，ケイ酸アルミニウム，水酸化アルミニウム，ケイ酸（サイロイド，エアロシル），メタケイ酸アルミン酸マグネシウム（ノイシリン），ステアリン酸マグネシウム，ステアリン酸アルミニウム，ステアリン酸ナトリウムなどの周期表第I,II,III族の金属の酸化物、水酸化物、無機酸塩または有機酸塩などの１種又は２種以上が用いられる。固体塩基の粒径は通常50μm以下好ましくは0.05～20μmである。固体塩基の使用量は全重量に対して通常１～80重量％、好ましくは１～50重量％、より好ましくは10～30重量％である。

また、塩基性薬効成分は、その水溶液が塩基性（たとえばpH7.0～13.0、好ましくは7.0～10.5）を示すものあるいは塩基性基（たとえばアミノ基等）を有するものであり、たとえばビンポセチン（vinpocetine）、エスタゾラム、アセタゾールアミド、パパベリン、トリプタミド、アセトヘキサミド、テオフィリン、ベラパミル、キニジン、プロプラノロール、モルフィン、エフェドリン、スコポラミン、クロルプロマジン、塩酸マニジピン等が用いられ、特にたとえばビンポセチン、アセタゾールアミド等が繁用される。そして、腸溶性物質としては、胃ではほとんど溶けなくて腸で始めて溶けるものが用いられるが、特に微粉末（10～0.05μm）のものを用いると好結果が得られる。この様な腸溶性物質としては、高分子（分子量30,000～500,000、好ましくは70,000～400,000）で酸性の化合物であってもよく、たとえばヒドロキシプロピルメチルセルロースフタレート、セルロースアセテートフタレート，カルボキシメチルエチルセルロース（CMEC AQ：興人社製），メタアクリル酸メタアクリル酸メチルコポリマー（オイドラギット（Eudragit） L100-55,オイドラギット L100,オイドラギット S100:レーム ファルマ“Rohm Pharma"社製，西ドイツ）などの酸性高分子の１種又は２種以上が用いられ、特にたとえばオイドラギット L100-55等が繁用される。腸溶性物質の粒径は通常50μm以下好ましくは0.05～10μmである。腸溶性物質は全重量に対して通常１～80重量％、好ましくは１～50重量％、より好ましくは10～30重量％である。

本発明のマトリックス剤においては上記のごとき酸性薬効成分及び塩基性薬効成分を含む薬効成分は、マトリックス剤全体の0.005～75重量％好ましくは0.01～50重量％含有させる。

本発明のマトリックス剤は、ポリグリセリン脂肪酸エステルまたはそれを含有してなる常温で固体のマトリックスに薬効成分を分散（以下固形のみならず液状の分散も含む）させてマトリックス特に細粒または顆粒にする、あるいはポリグリセリン脂肪酸エステルまたはそれを含有してなる常温で固体のマトリックスに酸性薬効成分と水に不溶ないし難溶の固体塩基とを分散させてマトリックス特に細粒または顆粒にする、あるいはポリグリセリン脂肪酸エステルまたはそれを含有してなる常温で固体のマトリックスに塩基性薬効成分と腸溶性物質とを分散させてマトリックス特に細粒または顆粒にすることにより製造することができる。たとえばポリグリセリン脂肪酸エステルまたはそれと常温で固体のマトリックスを作りうる上記のごとき添加剤とを加温（40～150℃好ましくは50～110℃）溶融したものに、薬効成分、あるいは酸性薬効成分と水に不溶ないし難溶の固体塩基、あるいは塩基性薬効成分と腸溶性物質を適量加えて分散させた後に冷却し、マトリックス特に細粒または顆粒とする等によって本発明の安定な放出制御性マトリックス剤特に細粒剤または顆粒剤を得ることができる。ポリグリセリン脂肪酸エステルを加温溶融する際に上記の脂質、添加剤を一緒に加温溶融させてもよく、また別々に加温溶融した後に混合してもよい。また、薬効成分と共に添加剤の粒子を加えることもできる。公知の造粒機等を用いて目的の細粒（通常500～10μmの粒子75重量％以上、500μm以上の粒子５重量％以下、10μm以下の粒子10重量％以下であり、好ましくは500～105μmの粒子75重量％以上、500μm以上の粒子５％重量以下、74μm以下の粒子10重量％以下である）、顆粒剤（たとえば1410～500μmの粒子90重量％以上、177μm以下の粒子５重量％以下である）等のマトリックス剤にすることができる。細粒剤を製造する場合は冷却下に細粒にするのが特によく、たとえば噴霧冷却、特にスプレーチリング等を行うことにより球形の細粒剤を得るのが好ましい。スプレーチリングは、たとえば通常10～6,000回転／分、好ましくは900～6,000回転／分、より好ましくは1,000～3,000回転／分の高速回転ディスク（たとえば直径５～100cm、好ましくは10～20cmの平滑円盤等であり、たとえばアルミ製円盤等）の上に一定流速（２～200g/分、好ましくは５～100g/分）で滴下する等により行うことができる。

本発明のマトリックス剤特に細粒剤又は顆粒剤は、たとえば表面改質、味のマスキング、腸溶性などの目的のため自体公知の方法でコーティングしたマトリックス剤としてもよい。そのコーティング基剤としては、たとえばヒドロキシプロピルメチルセルロース，エチルセルロース，ヒドロキシメチルセルロース，ヒドロキシプロピルセルロース，粉糖，ポリオキシエチレングリコール，ツィーン80，プルロニックF68，ヒマシ油，セルロースアセテートフタレート，ヒドロキシプロピルメチルセルロースフタレート，ヒドロキシメチルセルロースアセテートサクシネート，アクリル酸系ポリマー（オイドラギットL100-55，L-100，S-100，レーム　ファルマ社製，西ドイツ），カルボキシメチルエチルセルロース，ワックス類等のほか、タルク，酸化チタン，ベンガラ等の色素が用いられ、これら単独あるいは２種以上を組みあわせて一層あるいは二層にコーティングしてもよい。コーティングには、自体公知の方法が採用される。すなわちパンコーティング法，流動コーティング法，転動コーティング法などにより、コーティング基剤を水あるいは有機溶媒に分散あるいは溶解したものをたとえばスプレーする等により行なう。細粒剤は通常25～70℃好ましくは25～40℃でコーティングされるのがよい。

本発明の放出制御性マトリックス剤は細粒又は顆粒の形態が好ましいが、医療機関や服用者の便宜から、錠剤が求められる場合には、上記のごとくして得られるマトリックス剤特に細粒剤又は顆粒剤を、必要ならば賦形剤（とりわけ上記のごとき崩壊剤等）と共に常法に従ってたとえば0.2～2.0トン／cm²好ましくは0.2～1.0トン／cm²で打錠することにより錠剤を製することもでき、又細粒剤又は顆粒剤を常法によりカプセルに充填することによりカプセル剤とすることもできるが、これら錠剤、カプセル剤は本発明のマトリックス剤特に細粒剤又は顆粒剤と同じ優れた効果を有し、安定な放出速度を示す放出制御性錠剤又はカプセル剤が得られるが、この錠剤又はカプセル剤又は本発明の範囲に含まれる。

かくして得られる本発明のマトリックス剤の細粒剤、顆粒剤、錠剤及びカプセル剤等は、一般の細粒剤、顆粒剤、錠剤及びカプセル剤と同様にして用いることができ、たとえば薬効成分の対象患者（人、家畜、実験用動物等の哺乳動物）に経口的に投与すること等により使用できる。

「作用」

本発明のマトリックス剤の細粒剤、顆粒剤、錠剤及びカプセル剤は、医薬（薬効成分）の放出速度の変化しない極めて安定な放出制御性を有しており、長期間の保存後においても医薬の放出パターンにほとんど変化がないほか、薬物の味、臭いをマスキングすることもでき、薬物の溶出速度が制御し易い、適用薬物の範囲が広い、製造時には有機溶媒を必要とせず、製造過程で大気汚染を生じることなく、製剤に残留溶媒の危険性及び静電気の発生もなく、製造工程が簡便で特別な装置も必要とせず、従って放出制御性製剤としては理想的なものである。

「実施例」

つぎに実施例をあげて本発明を更に詳しく説明するが、本発明はかかる実施例のみに限定されるものではない。

後述の実施例における溶出速度の測定は次に示した方法によって行なった。すなわち、第十一改正日本薬局方

（以下日局11と略記する。）の溶出試験法の第２法（パドル法）に準じて、界面活性剤を添加した溶出液900ml中、パドル回転数100rpmで行い、経時的にサンプリングし、ろ過した液の吸光度から溶出率を算出した。

実施例１

ステアリン酸ペンタ（テトラ）グリセリド（阪本薬品（株）製:PS-310）80gを90℃に加温、融解し、20gのテオフィリンを投入して30分間撹拌し分散させた。これを90℃に加温し、2000rpmで回転している直径15cmのアルミ製ディスクに20g/分で滴下し、42メッシュの篩を通過し60メッシュの篩を通過しない（以下42/60メッシュと略記する）ところの球形の細粒剤を得た。

実施例２

ステアリン酸モノ（テトラ）グリセリド（阪本薬品（株）製:MS-310、以下"MS-310"と略称する。）37.5gと硬化綿実油42.5gとを90℃で加温、融解し、テオフィリン20gを投入して30分間撹拌分散させた以外は実施例１と同様にして（即ちスプレーチリング"Spray Chilling"して）42/60メッシュ球形の細粒剤を得た。

実施例３

MS-310	25g
硬化綿実油	55g
テオフィリン	20g

を用いて実施例２と同様にしてスプレーチリングし42/60メッシュの球形の細粒剤を得た。

実施例４

MS-310	125g
硬化綿実油	67.5g
テオフィリン	20g

を用いて実施例２と同様にしてスプレーチリングし42/60メッシュの球形の細粒剤を得た。

実施例５

MS-310	20g
硬化綿実油	40g
AD-5467	40g

を用いて実施例２と同様にしてスプレーチリングし32/42メッシュの球形の細粒剤を得た。

実施例６

MS-310	1g
硬化綿実油	109g
テオフィリン	90g

を用いて実施例２と同様にしてスプレーチリングし42/60メッシュの球形の細粒剤を得た。

実施例７

MS-310 1g、乳糖45g及び硬化綿実油110gを90℃で加温、融解し、テオフィリン45gを投入して30分間撹拌分散させた以外は実施例１と同様にしてスプレーチリングし42/60メッシュの球形の細粒剤を得た。

実施例８

MS-310	1g
ステアリルアルコール	100g
AD-5467	100g

を用いて実施例２と同様にしてスプレーチリングし48/60メッシュの球形の細粒剤を得た。

実施例９

実施例８で得られた細粒剤200g、アビセル75g、ECG505（崩壊剤：ニチリン化学社製）25g、ステアリン酸マグネシウム0.9gを混合し、直径11mmの杵（曲率半径15R）で0.2トン／cm^2で打錠して錠剤を得た。

実施例10

MS-310 5g、硬化綿実油20gを90℃で加温、融解し、ビンポセチン1g、オイドラギット L100-55 15gを投入して30分間撹拌分散させた後、実施例１と同様にしてスプレーチリングし42/60メッシュの球形の細粒剤を得た。

実施例11

MS-310 3g、硬化綿実油20g、ビンポセチン1g及びオイドラギット L100-55を用いて、実施例10と同様にして42/60メッシュの球形の細粒剤を得た。

実施例12

MS-310 7g、硬化綿実油21gを90℃で加温、融解し、AD-5467 5g、水酸化マグネシウム10gを投入して30分間撹拌分散させた後、実施例１と同様にしてスプレーチリングして42/60メッシュの球形の細粒剤を得た。

実施例13

水酸化マグネシウム10gの代りに合成ケイ酸アルミニウム10gを用いた以外は、実施例12と同様にして42/60メッシュの球形の細粒剤を得た。

実施例14

ステアリン酸ペンタ（テトラ）グリセリド（阪本薬品（株）製:PS-310）91gを加温（90℃）融解し、9gのイデベノンを投入して90℃に保って30分間撹拌し融解させた。実施例１と同様にして60/80メッシュの細粒剤を得た。

比較例として硬化綿実油91gと9gのイデベノンを用いて上記と同様にして42/60メッシュの細粒剤を得た。40℃に保存した場合のこれら細粒剤からの溶出率（％：以下断りない場合％は重量％を示す）を表１に示した。

表１

溶出率%		時間 1	2	3	4	5	6
PS-310を用いた細粒剤	製造直後	55.7	74.2	85.7	93.9	99.3	102.6
	40℃1カ月	60.8	73.3	82.2	88.6	92.9	96.5
	40℃2カ月	61.4	74.1	82.8	89.2	94.1	97.2
硬化綿実油を用いた細粒剤	製造直後	27.3	36.0	43.2	49.4	54.9	59.9
	40℃1カ月	33.0	44.0	53.0	61.0	68.0	74.0

この表１より、硬化綿実油を用いて得られた細粒剤からのイデベノンの40℃、１カ月後の溶出率は速くなっているのに比べ本発明のPS-310を用いた細粒剤からの溶出率は製造直後にくらべ40℃、１カ月後も変化は小さく更に２カ月後も変化していないので本発明の細粒剤の持続性が安定であることが明らかにされる。

実施例15

ステアリン酸ペンタ（テトラ）グリセリド（阪本薬品（株）製:PS-310）75g,ステアリン酸モノ（テトラ）グリセリド（阪本薬品（株）製:MS-310）5gを加温（90℃），融解させ、トレピブトン10g,酸化マグネシウム30gを投入し80℃に保って30分撹拌し分散させ、実施例１と同様にして42/60メッシュの球形の細粒剤を得た。日局11記載のＩ液,II液およびpH5中での溶出率を表２に示す。

表２

溶出率(%)	時間 1	2	3	4	5	6
Ｉ液(pH1.2)	19.4	29.4	37.1	43.8	50.0	54.7
pH 5	28.7	36.3	45.6	55.1	63.8	70.1
II液(pH6.8)	29.5	37.6	45.5	52.9	60.7	66.8

この表２より、本発明の細粒剤は、広いpH範囲においてほぼ同じ速度で薬物を放出するので、安定な放出制御性を示す細粒剤であることがわかる。

さらに、実施例15で得られた細粒剤を40℃,4カ月保存した後のＩ液およびII液中での溶出率を表３に示す。

表３

Ｉ液中

時間 / 溶出率	1	2	3	4	5	6
製造直後	19.4	29.4	37.1	43.8	50.0	54.7
40℃4カ月	18.9	30.0	38.1	44.2	49.2	53.7

II液中

時間 / 溶出率	1	2	3	4	5	6
製造直後	29.5	37.6	45.5	52.9	60.7	66.8
40℃4カ月	28.9	37.1	45.1	53.2	60.5	66.4

この表３より、本発明の細粒剤の放出制御性は、40℃,4カ月間の保存後でも製造直後と変わらない溶出率を示すことにより、極めて安定であることが分る。

実施例16

ステアリン酸ペンタ（テトラ）グリセリド（阪本薬品（株）製:PS-310）75.2g,ステアリン酸モノ（テトラ）グリセリド（阪本薬品（株）製:MS-310）20.8gを加温（90℃），融解し、ビンポセチン4gおよびオイドラギットL100-55（レーム　ファルマ社製，西ドイツ）60gを投入し80°に保って30分撹拌し分散させ、実施例１と同様にして42/60メッシュの球形の細粒剤を得た。日局11記載のＩ液およびII液（以下“Ｉ液”、“II液”と略称する）中での溶出を表４に示す。

表４

溶出率(%)	時間 1	2	3	4	5	6
Ｉ液(pH1.2)	43.4	63.2	75.1	83.5	89.8	95.1
II液(pH6.8)	48.9	64.7	71.5	75.4	79.1	83.6

この表４より、本発明の細粒剤は、pHの異なる環境においても同じ速度で薬物を放出することから、安定な放出制御性を示す細粒剤であることがわかる。

実施例17

ステアリン酸ペンタ（テトラ）グリセリド（阪本薬品（株）製:PS-310）75g,ステアリン酸モノ（テトラ）グリセリド（阪本薬品（株）製:MS-310）21gを加温（90℃），融解し、ビンポセチン4gおよびオイドラギットL100-55（レーム　ファルマ社製，西ドイツ）60gを投入し80°に保って30分間撹拌し分散させ、実施例１と同様にして42/60メッシュの球形の細粒剤を得た。Ｉ液,II液に40℃で２週間及び４カ月間保存した時の溶出率を表５に示す。

表５

Ｉ液中での溶出率

保存期間＼時間	1	2	3	4	5	6
製造直後	36.5	56.4	69.0	77.5	84.4	89.8
40℃ 2週	41.6	61.4	73.1	81.5	87.9	92.6
40℃4カ月	52.5	66.5	81.0	87.0	91.6	96.4

II液中での溶出率

保存期間＼時間	1	2	3	4	5	6
製造直後	57.7	73.8	79.3	82.5	85.9	88.5
40℃ 2週	55.6	69.3	75.1	79.8	83.6	87.1
40℃4カ月	58.7	72.1	84.4	87.4	92.0	92.3

この表５より、本発明の細粒剤は、40℃,2週後においても製造直後と変わらない安定な放出制御性細粒剤であり、その安定性は更に40℃,4カ月後も変化しないことが分る。

実施例18

ステアリン酸ペンタ（テトラ）グリセリド（阪本薬品（株）製:PS-310）75g,ステアリン酸モノ（テトラ）グリセリド（阪本薬品（株）製:MS-310）25gを加温（90℃），融解し、AD-5467 100gを投入し90°に保って30分間撹拌し分散させ、実施例１と同様にして42/80メッシュの細粒を得た。

実施例19

ステアリン酸ペンタ（テトラ）グリセリド（阪本薬品（株）製:PS-310）52g,ステアリン酸モノ（テトラ）グリセリド（阪本薬品（株）製:MS-310）4gを加温（90℃），融解し、AD-5467 10gおよび水酸化マグネシウム40gを投入し90°に保って30分間撹拌し分散させ、実施例１と同様にして42/60メッシュの球形の細粒剤を得た。得られた細粒剤をＩ液,II液で40℃に保存した後の溶出率を表６に示した。

表６

溶出率(%)		時間 1	2	3	4	5	6
Ｉ液	製造直後	54.1	69.8	77.6	91.1	96.7	99.5
	40℃1カ月	48.1	60.1	76.1	88.1	96.3	99.3
II液	製造直後	46.5	65.6	77.0	83.2	86.9	88.2
	40℃1カ月	47.3	70.5	80.7	86.1	86.4	86.4

この表６より、本発明の細粒剤は、40℃,1カ月後においても製造直後と変わらない溶出率を示す安定な放出制御性細粒剤であることが分る。

実施例20

ステアリン酸ペンタ（テトラ）グリセリド（阪本薬品（株）製:PS-310）192g,ステアリン酸モノ（テトラ）グリセリド（阪本薬品（株）製:MS-310）32gを加温（90℃），融解し、AD-5467 40gおよび水酸化マグネシウム1

60gを投入し90°に保って30分間撹拌して分散させ、実施例1と同様にして42/60メッシュの球形の細粒剤を得た。

実施例21

AD-5467	40g
PS-310	216g
MS-310	8g
水酸化マグネシウム	160g

を用いて実施例20と同様にして60/80メッシュの球形の細粒剤を得た。実施例20と21で得た細粒剤のI液,II液中での溶出率を表7に示した。また実施例20と21で得られたAD-5467含有細粒剤及び比較として5w/v%アラビアゴム水懸濁液にAD-5467を4mg/ml溶かした液をそれぞれ1群4匹のラット（SD系ラット,8週令雄）に投与した。投与量はいずれもAD-5467として10mg/kgで絶食下に投与し、血中濃度を測定し表7に示した。

表7

溶出率(%)	時間					
	1	2	3	4	5	6
実施例20 I液	66.5	89.3	97.5	100.0	100.0	100.0
〃 II液	76.7	88.5	90.5	90.3	90.6	90.8
実施例21 I液	36.6	50.0	58.8	65.9	71.7	76.3
〃 II液	36.8	48.4	71.8	78.5	81.8	82.5

この表7より、本発明の細粒剤は、pHの異なる環境においてもほぼ同じ速度でAD-5467が溶出し、またポリグリセリン脂肪酸エステルの組成比を変えることによってpHに影響されずにしかも速く溶出する細粒剤（実施例21）や遅く溶出する細粒剤（実施例20）に製造できることが分る。

表8

血中濃度 μg/ml	時間							
	0.25	0.5	1	1.5	2	3	5	7
実施例20	0.75	2.30	3.14	2.22	1.19	0.52	0.53	0.23
〃 21	0.16	0.73	0.88	1.12	1.23	0.79	0.57	0.69
5w/v%アラビアゴム水懸濁液	5.97	2.85	1.38	0.70	0.41	0.20	0.20	0.13

この表8は、AD-5467含有5%アラビアゴム水懸濁液を投与した場合は、15分でAD-5467の血中濃度はピークとなり急速に低下するのに比べて、本発明の実施例20の細粒剤の場合は1時間後に、実施例21の細粒剤の場合では2時間後にピークがあり本発明の細粒剤がすぐれた放出制御性を有していることを示している。

実施例22

ステアリン酸モノ（デカ）グリセリド（阪本薬品（株）製）92gを加温（90℃）融解し、イプリフラボン18gを投入し、90℃に保って30分間撹拌し、分散させ、実施例1と同様にして42/60メッシュの球形の細粒剤を得た。この細粒剤を絶食下ビーグル犬（1才雄、約10kg）4頭の各々にイプリフラボンとして200mgを経口投与してイプリフラボンの主代謝物である7－ヒドロキシ－3－フェニル－4H－1－ベンゾピラン－4－オン（7－hydroxy－3－phenyl－4H－1－benzopyran－4－one）の血中濃度を測定して表9に示した。対照としてイプリフラボン200mgを5w/v%アラビアゴム水懸濁液30mlに分散したもの（以下“サスペンション”と略す。）を用いた。

表9

血中濃度 ng/ml

	時間							
	0.25	0.5	1	1.5	2	3	5	7
実施例22	43.1	120.7	198	187.1	209.2	219.5	125.7	121.7
サスペンション	0.1	7.2	10.3	21.9	33.0	25.0	32.1	25.6

この表9より、実施例22で得られた本発明の細粒剤からのイプリフラボンの吸収は、サスペンションにくらべ約10倍高くしかも持続していることが分る。

実施例23

（1）ステアリン酸ペンタ（テトラ）グリセリド（阪本薬品（株）製:PS-310）860g,ステアリン酸モノ（テトラ）グリセリド（阪本薬品（株）製:MS-310）10gを加温（90℃）融解し、塩酸フェニールプロパノールアミン90gを投入して90℃に保ち、30分間攪拌して実施例1と同様にして30/42メッシュの球形の細粒剤を得た。

（2）上記（1）で得た細粒剤300gを流動層乾燥機（FD-3S:富士産業）に入れ吸気温度45℃，品温35℃にコントロールしてヒドロキシプロピルメチルセルロース（TC-5R:信越化学（株））の5w/w%水溶液を噴霧してコーティング細粒剤を得た。実施例23（1）と（2）で得た細粒剤からのフェニルプロパノールアミンの水中での溶出率を表10に示す。

表10

溶出率

時間	1	2	3	4
実施例23 細粒	22.9	31.3	37.8	38.6
〃 24 コーティング細粒	18.8	27.0	33.5	34.9

この表10より、本発明の細粒剤はコーティングした後も、もとの細粒剤とほぼ同じ溶出率を示し、安定な放出制御性を有していることが分る。

実施例24

（1）ステアリン酸ペンタ（テトラ）グリセリド（阪本薬品（株）製:PS-310）800g,ステアリン酸モノ（テトラ）グリセリド（阪本薬品（株）製:MS-310）100gを加温（90℃）融解し、カフェイン100gを投入して90℃に保って30分間攪拌し、分散させて、実施例1と同様にして42/60メッシュの球形の細粒剤を得た。

（2）上記（1）で得た細粒剤250gを流動層乾燥機（FD-3S:富士産業）に入れ吸気温度45℃，品温35℃にコントロールし、ヒドロキシプロピルメチルセルロースの5w/w%エタノール溶液を噴霧してコーティング細粒剤を得た。

実施例25

実施例24の（1）で得た細粒剤100g,アビセル90g,カルボキシメチルセルロースナトリウム（FMC－旭化成工業（株）,Ac-Di-Sol）10g,ステアリン酸マグネシウム0.6gを混合し直径10mmの杵（平面）で0.2ton/cm^{2}で打錠し錠剤を得た。

実施例24で得た細粒剤と実施例25で得た錠剤からのカフェインの溶出率を表11に示す。

表１１

溶出率(%)	時間					
	1	2	3	4	5	6
細　粒	16.1	24.5	33.4	38.3	43.8	46.5
ｺｰﾃｨﾝｸﾞ後錠剤	17.2	27.8	36.7	45.5	48.9	51.4

この表11より、本発明の細粒剤をコーティングし打錠した錠剤（実施例25）からのカフェインの溶出は、打錠前の細粒剤（実施例24）からと同じ速度で溶出すること、及び両製剤共に安定な放出制御性を示すことが分る。

実施例26

ステアリン酸ペンタ（テトラ）グリセリド（阪本薬品（株）製:PS-310）64g,ステアリン酸モノ（テトラ）グリセリド（阪本薬品（株）製:MS-310）16gを加温（90℃），融解し、塩酸デラプリル20gを投入して70℃に保って30分間撹拌し、分散させて、実施例１と同様にして60/80メッシュの球形の細粒剤を得た。得られた細粒剤からの塩酸デラプリルの溶出率を表13に示した。また、得られた細粒剤を塩酸デラプリルとして20mg/kgをラットに絶食下投与して、薬効を示す塩酸デラプリルの代謝物である、ジカルボン酸体［Ｎ－［Ｎ－［（Ｓ）－１－カルボキシ－３－フェニルプロプル］－Ｌ－アラニル］－Ｎ－インダン－２－イル）グリシン（Ｎ－［Ｎ－［（Ｓ）－１－carboxy－３－phenylpropyl］－Ｌ－alanyl］－Ｎ－indan－２－yl）glycine）］の血中濃度を表14に示した。対照として5w/v%アラビアゴム水懸濁液に塩酸デラプリルを4mg/ml溶かした液を用いた。

表１３

溶出率(%)	時間					
	1	2	3	4	5	6
60/80ﾒｯｼｭ細粒剤	48.3	74.1	85.5	90.1	92.3	93.0

この表13より、本発明の60/80メッシュの細粒剤は良好な持続性の溶出を示すことが分る。

表１４

血中濃度μg／ml

	時間							
	0.25	0.5	1	1.5	2	3	5	7
６０／８０メッシュ細粒剤	0.881	0.816	0.785	0.647	1.07	0.387	0.115	0.052
塩酸デラプリルの５w/v%アラビアゴム水懸濁液	5.46	4.63	0.875	0.427	0.221	0.200	0.090	0.007

この表14は、塩酸デラプリルの５％アラビアゴム水溶液をラットに投与した場合、0.25時間に速やかに消失しているのに対し、本発明の細粒剤は溶出速度に応じた持続した血中濃度を示すことが分る。

実施例27

ステアリン酸モノ（テトラ）グリセリド8g（阪本薬品（株）製:MS-310），ステアリン酸ペンタ（テトラ）グリセリド32g（阪本薬品（株）製:PS-310）およびステアリン酸トリ（テトラ）グリセリド40g（阪本薬品（株）製:TS-310）を加温，融解し、70℃に調整し、塩酸デラプリル20gを投入して30分間攪拌し分散させた。実施例１と同様にして42/60メッシュの細粒剤を得た。

実施例28

実施例27で得られた細粒250gを流動層乾燥機（FD-3S:富士産業）に入れ吸気温度45℃，品温35℃にコントロールし、ヒドロキシプロピルセルロースの5w/w%エタノール溶液を噴霧してコーティングしコーティング細粒剤を得た。

実施例29

実施例28で得られたコーティング細粒剤100g,アビセル90g,カルボキシメチルセルロースナトリウム（FMC－旭化成工業（株）:Ac-Di-Sol）10g,ステアリン酸マグネシウム0.6gを混合し、直径10mmの杵（平面）で0.2ton/cm²で打錠して錠剤を得た。

実施例27,28および29の細粒剤，コーティング細粒剤，錠剤からの塩酸デラプリルの溶出率を表15に示す。

表１５

溶出率(%)	時間					
	1	2	3	4	5	6
実施例２７	56.9	83.3	89.8	89.9	89.2	90.6
実施例２８	51.5	78.4	89.2	92.6	93.1	92.5
実施例２９	62.9	85.9	89.5	91.0	91.9	92.5

この表15より、本発明のコーティングした細粒剤，コーティング細粒剤を打錠した錠剤からの塩酸デラプリルの溶出はもとの細粒剤と変わらず、安定かつ持続した溶出を示すことが分る。

実施例30

ステアリン酸ペンタ（テトラ）グリセリド（阪本薬品（株）製:PS-310）65.6g,ステアリン酸モノ（テトラ）グリセリド（阪本薬品（株）製:MS-310）9.4gを加温（90℃），融解し、塩酸デラプリル25gを投入し、70℃に保って30分間撹拌し、分散させて、実施例１と同様にして42/60メッシュの球形の細粒剤を得た。得られた細粒剤を40℃保存した時のII液での塩酸デラプリルの溶出を表16に示す。

表１６

保存期間＼時間	1	2	3	4	5	6
製造直後	38.4	57.1	74.3	83.2	85.7	86.8
40℃ 10日	38.9	58.8	73.2	80.7	83.8	84.1
40℃ 3.5カ月	35.8	53.2	66.2	74.5	79.0	81.7

この表16より、本発明の細粒剤は、長期の保存後においても優れた放出制御性を有しており、極めて安定な放出制御性製剤であることが分る。

実施例31

実施例17で得られた細粒剤を１号カプセルに充填してカプセル剤を得た。

実施例32

実施例18で得られた細粒剤を直径6mmの杵（平面）で0.1ton/cm²で打錠して錠剤を得た。

実施例33

ステアリン酸ペンタ（テトラ）グリセリド（阪本薬品（株）製:PS-310）800g,ステアリン酸モノ（テトラ）グリセリド（阪本薬品（株）製:MS-310）100g,カフェイン100gを用いてディスクの回転数を900rpmとした以外は実施例24の（１）と同様にして、12/48メッシュの顆粒を得た。

「発明の効果」

本発明の製剤は極めて安定な放出制御性を有しているので、医薬の投与回数をへらす、副作用を軽減する等が可能になる。

フロントページの続き

(58)調査した分野(Int.Cl.^{6}，ＤＢ名)
A61K 47/14,47/34
A61K 9/16,9/22

Corresponding US Application of (1)

US005399357A

United States Patent [19]

Akiyama et al.

[11] **Patent Number: 5,399,357**

[45] **Date of Patent: Mar. 21, 1995**

[54] **SUSTAINED RELEASE PREPARATIONS**

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[21] Appl. No.: **807,630**

[22] Filed: **Dec. 13, 1991**

Related U.S. Application Data

[63] Continuation of Ser. No. 433,223, Nov. 8, 1989, abandoned.

[30] **Foreign Application Priority Data**

Nov. 8, 1988	[JP]	Japan	63-282994
Nov. 21, 1988	[JP]	Japan	63-294379
Oct. 3, 1989	[JP]	Japan	1-259674

[51] **Int. Cl.**^{6} **A61K 9/16**; A61K 9/26; A61K 9/50; A61K 47/34

[52] **U.S. Cl.** **424/457**; 424/486; 424/458; 424/459; 424/461; 424/462; 424/470; 424/490; 424/494; 424/495; 424/497; 424/501; 514/785; 514/951; 514/963; 514/965

[58] **Field of Search** 424/458, 470, 486, 501; 514/785, 965, 963, 951

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[57] **ABSTRACT**

There is provided a matrix preparation produced by dispersing a pharmaceutically active ingredient into a matrix which is solid at ambient temperature and comprised of a fatty acid ester of a polyglycerol. The preparation has stable release controlling ability, can be processed to fine granules, granules, capsules, tablets etc., and contributes to reduction of the administration times of the active ingredient and side effects of the ingredient.

16 Claims, No Drawings

SUSTAINED RELEASE PREPARATIONS

This application is a continuation of U.S. application Ser. No. 07/433,223, filed Nov. 8, 1989, now abandoned.

The present invention relates to stable, controlled release matrix preparations.

For the purposes of reducing a number of doses while sustaining the effect of a drug, and suppressing rapid elevation of drug concentration in blood to thereby alleviate side-effects or retaining drug concentration in blood for a long time, controlled release preparations, particularly sustained release pharmaceutical preparations have been studied with a variety of drug substances and by means of a number of methods. The controlled release preparations include, for example, capsule-type dosage forms comprising a drug-containing core portion covered with a membrane and matrix-type dosage forms consisting of a drug dispersed in the drug-release controlling layer.

These conventional controlled release preparations, which are required to be subjected to more sophisticated processing techniques, have been provided in the forms of tablets, capsules or granules.

Taking into consideration the fact that a recently increasing number of aged persons and children are given medicine, however, controlled release preparations in the form of fine granules are regarded desirable. In addition, one of the advantages that fine granules can offer lies in that their doses can be easily adjusted. However, stable controlled release preparations, particularly fine granules have not been obtainable, as far as they are produced in accordance with a production process for conventional controlled release preparations. Therefore, no controlled release fine granules have been commercialized so far in the past.

Under these circumstances, the present inventors conducted extensive investigation into a controlled release matrix preparation which can be prepared by means of a practical and economical production method without the use of a solvent harmful to human beings, can also be easily adjusted in dissolution rate, is easy for patients to take and stable. As a result, the present inventors found that when an active ingredient is dispersed into a matrix being solid at ambient temperature (15° to 35° C.) and consisting of or containing a fatty acid ester of a polyglycerol, which has not been employed in conventional matrix preparations, to produce a matrix preparation, particularly fine granules, an ideal controlled release matrix preparation can be obtained unexpectedly. The matrix preparation thus obtained excels remarkably in not only stability and release-controlling ability but also economy, toxicity, effect, etc. and furthermore that when a pharmaceutically active acidic ingredient and a solid base being insoluble or slightly soluble in water, or an active basic ingredient and an enteric substance, are dispersed during the production process for the matrix preparation as described above, there can be obtained controlled release fine granules being provided with pH-independence, which allows an active ingredient to dissolve in the stomach and intestine at a constant rate. In addition to the above excellent characteristics, the resultant matrix preparations are suited for commercialization. The fine granules described here have been named Micromatrix system (MMS).

These findings have led the inventors to the completion of this invention.

Thus, this invention relates to:

1. A matrix preparation which comprises a pharmaceutically active ingredient dispersed into a matrix being solid at ambient temperature and consisting of a fatty acid ester of a polyglycerol or containing the same.

2. Fine granules or granules which comprise a pharmaceutically active ingredient dispersed into a matrix being solid at ambient temperature and consisting of a fatty acid ester of a polyglycerol or containing the same.

3. A matrix preparation according to the item 1, wherein microcrystalline wax is contained in the matrix.

4. Fine granules or granules according to the item 2, wherein microcrystalline wax is contained in the matrix.

5. Fine granules or granules according to the item 2 or 4, wherein the fine granules or granules are coated with a coating agent.

6. Capsules wherein the fine granules or granules according to the item 2 or 5 are filled.

7. Tablets which are produced by tabletting the fine granules or granules according to the item 2 or 5.

8. Tablets according to the item 7, which contain a disintegrating agent.

9. Fine granules or granules which comprise a pharmaceutically active acidic ingredient and a water-insoluble or slightly water-soluble solid base dispersed into a matrix being solid at ambient temperature and consisting of a fatty acid ester of a polyglycerol or containing the same.

10. Fine granules or granules which comprise a pharmaceutically active basic ingredient and an enteric substance dispersed into a matrix being solid at ambient temperature and consisting of a fatty acid ester of a polyglycerol or containing the same.

11. Fine granules or granules according to the item 9 or 10, which are coated with a coating agent.

12. Capsules wherein the fine granules or granules according to the item 9, 10 or 11 are filled.

13. Tablets which are produced by tabletting the fine granules or granules according to the item 9, 10 or 11.

14. Tablets according to the item 13, wherein a disintegrating agent is contained.

The fatty acid ester of a polyglycerol in this invention is an ester formed by the combination of polyglycerol with a fatty acid. Polyglycerol is "a polyhydric alcohol having n (in a cyclic polyglycerin)—n+2 (in a straight or branched polyglycerin) hydroxyl groups and n−1 (in a straight or branched polyglycerin)—n (in a cyclic polyglycerin) ether combinations in one molecule" (Polyglycerin esters, p. 12, May 20, 1986, edited by Sakamoto Yakuhin Kogyo Co., Ltd., Japan). As the polyglycerol, there can be used, for example, those represented by the formula:

$$HO{+}CH_2-\underset{\displaystyle OH}{\underset{|}{C}H}-CH_2-O{+}_{n}H \qquad [I]$$

(wherein n is a degree of polymerization.). Normally, n is an integer of 2 to 50, preferably 2 to 20, more preferably 2 to 10. As specific examples of such polyglycerols, there are used, for example, diglycerol, triglycerol, tetraglycerol, pentaglycerol, hexaglycerol, heptaglycerol, octaglycerol, nonaglycerol, decaglycerol, pentadecaglycerol, eicosaglycerol and triacontaglycerol, and among others, frequent use is made of tetraglycerol, hexaglycerol and decaglycerol. As the

fatty acid, there can be used, for example, saturated or unsaturated higher fatty acids having a number of carbon atoms of 8 to 40, preferably 12 to 22. As the fatty acids, there are used, for example, palmitic acid, stearic acid, oleic acid, linolic acid, linoleic acid, myristic acid, lauric acid, ricinoleic acid, caprylic acid, capric acid and behenic acid, and among others, frequent use is made of stearic acid, oleic acid, lauric acid, ricinoleic acid, and the like. As the fatty acid esters of polyglycerols, there are used monoesters or polyesters from the polyglycerols and fatty acids as mentioned above. Such fatty acid esters of polyglycerols have ordinarily a molecular weight of 200 to 5000, preferably 300 to 2000, and an HLB (hydrophilic-lipophilic balance) of 1 to 22, preferably 1 to 15. Also, the fatty acid esters of polyglycerols can suitably be selected depending upon the type of active ingredients utilized, and there may be used, for example, those being capable of melting by warming active ingredients in proportions of 0.00001 to 5 g/ml, preferably 0.0001 to 1 g/ml. As specific examples of the fatty acid esters of polyglycerols, there may be used, for example, caprylyl di(tri)glyceride, capryl di(tri)glyceride, caprylyl mono(deca)glyceride, lauryl mono(deca)-glyceride, lauryl mono(hexa)glyceride, lauryl mono(-tetra)glyceride, oleyl di(tri)glyceride, oleyl di(tetra)-glyceride, linolyl di(tri)glyceride, linolyl di(tetra)glyceride, linolyl di(hexa)glyceride, linolyl di(hepta)glyceride, stearyl mono(deca)glycertide, stearyl deca(deca)-glyceride, stearyl mono(tetra)glyceride, stearyl mono(-tetra)glyceride, stearyl mono(hexa)glyceride, stearyl sesqui(hexa)glyceride, oleyl sesqui(deca)glyceride, oleyl penta(hexa)glyceride, stearyl tri(hexa)glyceride, stearyl penta(hexa)glyceride, oleyl mono(hexa)glyceride, lauryl mono(deca)glyceride, stearyl tri(tetra)-glyceride, stearyl penta(tetra)glyceride, oleyl mono(tetra)glyceride, oleyl penta(tetra)glyceride, lauryl mono(-tetra)glyceride, palmityl mono(deca)glyceride, palmityl deca(deca)glyceride, palmityl mono(hexa)glyceride, palmityl sesqui(hexa)glyceride, palmityl tri(hexa)glyceride, palmityl penta(hexa)glyceride, palmityl mono(tetra)glyceride, palmityl tri(tetra)glyceride, palmityl penta(tetra)glyceride, and the like, either solely or in mixtures of more than two kinds thereof, and among others, frequent use is made for example of stearyl penta(tetra)-glyceride (e.g., PS-310 produced by Sakamoto Yakuhin Co. of Japan), stearyl mono(tetra)glyceride (e.g., MS-310 produced by Sakamoto Yakuhin Co., Japan), stearyl penta(hexa)glyceride (e.g., PS-500 produced by Sakamoto Yakuhin Co., Japan) and stearyl sesqui(hexa)-glyceride (e.g., SS-500 produced by Sakamoto Yakuhin Co. of Japan), stearyl mono(deca)glyceride, etc. Particularly, in the case of the fatty acid ester of a polyglycerol is stearyl mono(deca) glyceride, excellent absorption of pharmaceutical active ingredient and stable controlled release ability are attained. These fatty acid esters of polyglycerols are used in such quantities as may correspond to about 0,001 to 50 times the weight of the active ingredient, preferably 0.005 to 5 times, however, the dose is not limited as far as the object of the invention is achieved.

In this invention matrixes containing fatty acid esters of polyglycerols are in the solid form at ambient temperature. The matrixes may best be incorporated with the fatty acid esters of polyglycerols as described above in such quantities as mentioned previously. As the matrix employable in this invention, there are used matrixes which are in the solid form at ambient temperature and have low melting points (30° to 150° C., preferably 40° to 120° C.). These matrixes can be incorporated, for example, with lipids in addition to the fatty acid esters of polyglycerols to thereby produce more preferred results. As these lipids, there are used pharmaceutically acceptable, water-insoluble lipids which demonstrate an action to regulate a dissolution rate of drugs, preferably lipids having a softening point or melting point of 40° to 120° C., preferably 40° to 90° C. As specific examples of these lipids, there are used for example hydrogenated oils (e.g., castor oil, cotton seed oil, soybean oil, rapeseed oil, beef tallow, and the like), beeswax, carnauba wax, spermaceti paraffin, lecithin, microcrystalline wax, fatty acids such as stearic acid and palmitic acid, or their salts (e.g., sodium salts, potassium salts, and the like), aliphatic alcohols such as stearyl alcohol and cetyl alcohol, and glycerides, among others. Frequent use is made for example of hardened cotton seed oil, hardened castor oil, hardened soybean oil, carnauba wax, stearic acid, stearyl alcohol and microcrystalline wax. The lipids may be used in an amount not hindering the object of the invention and normally they are used in such quantities as may correspond to about 0.01 to 100 times the weight of the active ingredient, preferably 1 to 20 times.

The matrixes being solid at ambient temperature usable in this invention can suitably be incorporated with additives being generally employable in the production of fine granules or granules, unless there is particular hindrance. For example, there can suitably be used excipients, such as lactose, corn starch, Avicel ®, powdered sugar and magnesium stearate; binding agents, such as starch, sucrose, gelatin, powdered gum arabic, methylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose and polyvinylpyrrolidone; disintegrating agents, such as calcium carboxymethylcellulose and substituted hydroxypropylcellulose; and other additives, such as coloring agents, flavoring agents, adsorbents, preservatives, wetting agents, antistatic agents and disintegration prolonging agents.

As the parmaceutically active ingredient, there may be employed drugs having relatively higher melting points (not lower than 121° C.), such as phenylpropanolamine hydrochloride, chlorphenylamine maleate, phenylephrine hydrochloride, theophylline, caffeine, procaineamide hydrochloride, sulfanylamide, cephalexin, ampicillin, molsidomine, indomethacin, sulfisoxazole, sulfadiazine, diazepam, valproic acid, quinidine sulfate, aspirin and 3,4-dihydro-2,8-diisopropyl-3-thioxo-2H-1,4-benzoxadine-4-acetic acid (hereinafter referred to as "AD-5467"), delapril hydrochloride, ipriflavone, trepibutone and the like; drugs having relatively lower melting points (about 0 to 120° C., preferably e.g. 40° to 120° C.), such as isosorbide nitrate, ketoprofen, cyclanderate, idebenone and 2-(12-hydroxydodeca-5,10-dinyl)-3,5,6-trimethyl-1,4-benzoquinone (hereinafter referred to as "AA-861"), and or proteins such as insulin, vasopressin, interferon, IL-2, urokinase a.FGF (acidic fibroblast growth factor), b.FGF (basic fibroblast growth factor) etc. The matrix preparation of the present invention can permit these drugs to gradually dissolve or/and be absorbed in the digestive tracts.

The solubility and absorption from the gastrointestinal tract of active ingredients vary with physicochemical properties. Generally speaking, base active ingredients, which show an increased solubility in the acid pH range but a decreased solubility in the alkali pH range, dissolve rapidly in the stomach so that they pass through under the influence of acid gastric juice, but

dissolve slowly in the neutral to weakly alkaline intestine. On the other hand, acid active ingredients, which exhibit an enhanced solubility in the alkaline pH region but a lower solubility in the acid pH region, dissolve rapidly in the neutral to weakly alkaline intestine but dissolve slowly in the stomach so that they pass through under the influence of acid gastric juice. Accordingly, in order to retain the appropriate controlled release dissolution of the active ingredient in the pH-independent manner so that its dissolution may be realized at a constant rate in both the stomach and intestine, in this invention, the acid active ingredient and water-insoluble or slightly water-soluble solid base, or the base active ingredient and enteric substance, are dispersed into the matrix of the fatty acid ester of a polyglycerol or the matrix containing the same which is in the solid form at ambient temperature.

The acid active ingredient as mentioned herein is that of which aqueous solutions present acidity (e.g. pH of not less than 1.5 but less than 7.0, preferably 2.0 to 6.8), or that which has acid group(s) (e.g. carboxyl group etc.). As the-ingredient, there may be used, for example, indomethacin, salicylic acid, AD-5467, trepibutone, aspirin, valproic acid, ketoprofen, ibuprofen, epinephrine, haloperidol, reserpine, ascorbic acid, acetaminophen and probenecide and AD-5467; trepiptone, indomethacin, and the like are among others preferably used. The solid base used includes water-insoluble or slightly water-soluble (solubility in water at 37° C. of not more than 0.1 g/ml, preferably not more than 0.001 g/ml) solid bases, whereupon the less soluble ones can produce more desirable results. As these solid bases, there are used oxides, hydroxides, inorganic acid salts or organic acid salts of metals of Groups I, II and III in the periodic table, either solely or in mixtures of not less than two kinds thereof, such as magnesium oxide, magnesium hydroxide, magnesium silicate, magnesium carbonate, aluminum silicate, aluminum hydroxide, silicic acid (cyloid, aerosol), magnesium aluminometasilicate (neusiline), magnesium stearate, aluminum stearate and sodium stearate. The solid bases have normally a particle size of not more than 50 μm, preferably 0.05 to 20 μm, while they are used in the proportions of usually 1 to 80 weight %, preferably 1 to 50 weight %, more preferably 10 to 30 weight %, to the total amount.

The basic active ingredient is that of which aqueous solutions present alkalinity (pH 7.0 to 13.0, preferably 7.0 to 10.5), or that which has basic group(s) (e.g. amino group etc.). As the ingredient, there are used, for example, vinpocetine, estazolam, acetazolamide, papaverine, tolbutamide, acetohexamide, theophylline, verapamil, quinidine, propranolol, morphine, ephedrine, scopolamine, chlorpromazine, manidipin hydrochloride, and the like with vinpocetine, acetazolamide, and the like being among others frequently used. As the enteric substance, there are used substances which hardly dissolve in the stomach but start to dissolve in the intestine, whereby finely powdered (10 to 0.05 μm) substances as used can particularly produce desired results. Such enteric substances may be acidic compounds of high molecular weights (molecular weights ranging from 30,000 to 500,000, preferably from 70,000 to 400,000), and there are used, for example, hydroxypropylmethylcellulose phthalate, cellulose acetate phthalate, carboxymethylethylcellulose (CMEC AQ®; produced by Kojin Co., Japan), methacrylic acid/methyl methacrylate copolymers (Eudragit ® L100-55, Eudragit L-100, Eudragit S-100; produced by Rohm Pharma Co., West Germany) and the like, either solely or in mixtures of not less than two kinds of these acidic high molecular weight. Particularly, Eudragit L100-55, and the like are frequently used. The enteric substances normally show a particle size of not more than 50 μm, preferably 0.05 to 10 μm, while they are used in proportions of usually 1 to 80 weight %, preferably 1 to 50 weight %, more preferably 10 to 30 weight %, to the total weight.

The active ingredients inclusive of the above-mentioned acid and basic active ingredients are contained in the matrix preparation of this invention in the proportions of 0.005 to 75 weight %, preferably 0.01 to 50 weight %, to the total weight of the fine granules.

The matrix preparation of this invention can be produced by dispersing (the term "disperse" includes the dispersion of not only solid but also liquid substances) an active ingredient into a matrix of a fatty acid ester of a polyglycerol or a matrix containing the same which is in the solid form at ambient temperature, followed by bringing to fine granules or granules; dispersing an acid active ingredient and a water-insoluble or slightly water-soluble solid base into a matrix of a fatty acid ester of a polyglycerol or a matrix containing the same which is in the solid form at ambient temperature, followed by bringing to fine granules or granules; or dispersing a basic active ingredient and an enteric substance into a matrix of a fatty acid ester of a polyglycerol or a matrix containing the same which is in the solid form at ambient temperature, followed by bringing to fine granules or granules. Thus, the stable, controlled release matrix preparations, particularly fine granules or granules of present invention can be obtained for example by melting by warming (40° to 150° C. preferably 50° to 110° C.) a fatty acid ester of a polyglycerol alone or in conjunction with the above-mentioned additives being capable of forming with it a matrix being solid at ambient temperature, adding to the melted substance an active ingredient, an acid active ingredient and a water-insoluble or slightly water-soluble solid base or a basic active ingredient and an enteric substance in suitable amounts to produce a dispersion, followed by cooling and bringing to a matrix, particularly fine granules or granules. When the fatty acid ester of a polyglycerol is melted by warming, the above-described lipid and additives may be melted be warming together with it or may be melted individually and then mixed with it. In addition, the active ingredient as well as particles of the additives can be added simultaneously. A known granulator can be employed to produce the objective matrix, such as fine granules (normally composed of not less than 75 weight % of particles of 500 to 10 μm, not more than 5 weight % of particles of not less than 500 μm and not more than 10 weight % of particles of not more than 10 μm; particularly not less than 75 weight % of particles of 500 to 105 μm, not more than 5 weight % of particles of not less than 500 μm and not more than 10 weight % of particles of not more than 74 μm), granules (composed of, for example, not less than 90 weight % of particles of 1410 to 500 μm and not more than 5 weight % of particles of not more than 177 μm) and the like.

Granulation under cooling is particularly preferred for producing fine granules, and for example, it is desirable to produce spherical fine granules through spray cooling, in particular through spray-chilling. Spray chilling can be performed for example by dripping or adding dropwise the melted material at a constant rate (2 to 200 g/min., preferably 5 to 1.00 g/min.) onto a

high-speed rotating disc (e.g., a smooth or flat disc, such as a disc made of aluminum, having 5 to 100 cm in diameter, preferably 10 to 20 cm) at a rotation number of usually 10 to 6,000 rpm, preferably 900 to 6,000 rpm, more preferably 1,000 to 3,000 rpm.

Present matrix preparations, particularly fine granules or granules may be those coated with a coating agent by a per se known method for reforming their surfaces, masking their taste or giving them a solubility in the intestine etc. As the coating agent, there are used, for example, hydroxypropylmethylcellulose, ethylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, sugar powder, polyoxyethylene glycol, Tween 80, Pluronic F 68, castor oil, cellulose acetate phthalate, hydroxypropylmethylcellulose acetate succinate, acrylic acid polymer (e.g. Eudragit ® L100-55, L-100, S-100, produced by Rohm Pharma Co., West Germany), carboxymethylcellulose, polyvinylacetyl, diethylaminoacetate, waxes, and the like, as well as pigments, such as talc, titanium oxide, red ochre etc. These agents may be used solely or in combination of two kinds or more to make one or two layers of coating. For the coating, there can be employed a per se known method. Namely, the coating may be carried out by, for example, spraying a liquid made by dispersing or dissolving the coating agent in water or an organic solvent on a matrix by pan-coating, fluidized coating or centrifugal fluidized coating.

The coating of fine granules is preferably carried out at a temperature of 25° to 70° C., preferably 25° to 40° C.

The controlled release matrix preparations preferably take the form of fine granules or granules but in cases where persons involved in the medical service or patients ask for tablets for the purpose of convenience, the matrix, preferably the fine granules or granules as obtained by the above procedure can be compressed to tablets, together with excipients (among others, disintegrating agent, etc. as mentioned above) added, if necessary, in accordance with the conventional method at a pressure of, for example, 0.2 to 2.0 ton/cm^2, preferably 0.2 to 1.0 ton/cm^2. Furthermore, the fine granules or granules can be filled into capsules by a conventional manner to process to capsule preparations. These tablets or capsules have excellent effects and stable release rate equal to the present matrix preparations, particularly fine granules or granules; however, it is to be understood that such tablets and capsules are included in the scope of the present invention.

The present matrix preparations of fine granules, granules, tablets, capsules etc. obtained by the above procedures can be put into use in the same manner as the conventional fine granules, granules, tablets, capsules, and the like, for example, by administering them orally to subjects (mammals, such as human beings, domestic animals and experimental animals) in whom the active ingredient is intended to be used.

The present matrix preparations of fine granules, granules, tablets and capsules possess the extremely stable controlled release ability being free from variation in drug (active ingredient) release rate and hardly show any change in the drug release pattern even after storage for a prolonged period of time, and further a bad taste or odor of a drug can be masked in the preparation. Moreover, the present preparations are easy to use to control the drug release rate, are applicable to a wide range of drugs, do not require the use of an organic solvent in the production process, do not cause air pollution in the production steps, do not provide any risk of solvent remaining in the pharmaceutical preparations nor produce any static electric charge and can be produced by the simplified production process requiring no special equipment, and consequently can be said to be the ideal controlled release preparations.

Described in the following are the examples to illustrate this invention in more particularly, but this invention is not understood to be not limited to such examples.

In the following examples, the dissolution rate was determined by the method referred to below;

According to Method 2 (paddle method) of "The Method for Determining Dissolution" in Japanese Pharmacopoeia, 11th Edition (herein after referred as "J.P. 11 Ed."), the dissolution from a test material was carried out in 900 ml of dissolution medium containing a surfactant under 100 rpm of revolution; sampling of the medium was carried out periodically, and the dissolution rates were calculated on the basis of UV-absorbance of each filtrate of the samples.

EXAMPLE 1

A 80 g quantity of stearyl penta(tetra)glyceride (PS-310^R produced by Sakamoto Yakuhin Co., Japan; hereinafter referred to as PS-310) was warmed and melted at 90° C., and 20 g of theophylline was put into the molten material, followed by stirring for 30 minutes to achieve dispersion. The dispersion was warmed at 90° C. and dripped at a rate of 20 g/min. onto an aluminum-made disc of 15 cm in diameter revolving at 2000 rpm. to produce spherical fine granules which passed through a 42 mesh sieve but did not pass through a 60 mesh sieve (hereinafter described briefly as "42/60 mesh").

EXAMPLE 2

By following the same procedure as described in Example 1 (namely through spray chilling), except that 37.5 g of stearyl mono(tetra)glyceride (MS-310 ® produced by Sakamoto Yakuhin Co., Japan; hereinafter referred to as MS-310) and 42.5 g of hydrogenated cotton seed oil were warmed and molten at 90° C. and 20 g of theophylline was put into the molten material, followed by stirring for 30 minutes to allow dispersion. There were obtained 42/60 mesh spherical fine granules.

EXAMPLE 3

By conducting spray chilling in the same manner as described in Example 2 while using:

25 g of MS-310
55 g of hydrogenated cotton seed oil
20 g of theophylline,

there were obtained 42/60 mesh spherical fine granules.

EXAMPLE 4

By carrying out spray chilling in the same manner as described in Example 2 while using:

125 g of MS-310
67.5 g of hydrogenated cotton seed oil
20 g of theophylline,

there were obtained 42/60 mesh spherical fine granules.

EXAMPLE 5

By conducting spray chilling in the same manner as described in Example 2 while using:

20 g of MS-310
40 g of hydrogenated cotton seed oil

40 g of 3,4-dihydro-2,8-diisopropyl-3-thioxo-2H-1,4-benzoxazine-4-acetic acid,

there were obtained 32/42 mesh spherical fine granules.

EXAMPLE 6

By conducting spray chilling in the same manner as described in Example 2 while using:

1 g of MS-310

109 g of hydrogenated cotton seed oil

90 g of theophylline,

there were obtained 42/60 mesh spherical fine granules.

EXAMPLE 7

By carrying out spray chilling in the same manner as described in Example 1, except that 1 g of MS-310, 45 g of lactose and 110 g of hydrogenated cotton seed oil were warmed and melted at 90° C. and 45 g of theophylline was put into the molten material, followed by stirring for 30 minutes to allow dispersion, there were obtained 42/60 mesh spherical fine granules.

EXAMPLE 8

By conducting spray chilling in the same manner as described in Example 2 while using:

1 g of MS-310

100 g of stearyl alcohol

100 g of 3,4-dihydro-2,8-diisopropyl-3-thioxo-2H-1,4-benzoxazine-4-acetic acid,

there were obtained 48/60 mesh spherical fine granules.

EXAMPLE 9

Mixed were 200 g of the fine granules as obtained in Example 8, 75 g of Avicel®, 25 g of ECG 505 ® (a disintegrating agent produced by Nichirin Chemical Co. of Japan) and 0.9 g of magnesium stearate, and the mixture was compressed into tablets at a pressure of 0.2 ton/cm^2 with the use of a punch of 11 mm in diameter (radius of curvature of 15R).

EXAMPLE 10

By conducting spray chilling in the same manner as described in Example 1 after warming and melting 5 g of MS310 and 20 g of hydrogenated cotton seed oil at 90° C., charging 1 g of vinpocetine and 15 g of Eudragit L100-55 into the molten material and stirring the mixture for 30 minutes to allow dispersion, there were obtained 42/60 mesh spherical fine granules.

EXAMPLE 11

By following the same procedure as described in Example 10 while using 3 g of MS-310, 20 g of hydrogenated cotton seed oil, 1 g of vinpocetine and Eudragit L100-55, there were obtained 42/60 mesh spherical fine granules.

EXAMPLE 12

By conducting spray chilling in the same manner as described in Example 1 after warming and melting 7 g of MS-310 and 21 g of hydrogenated cotton seed oil at 90° C., charging 5 g of AD-5467 and 10 g of magnesium hydroxide and stirring the mixture for 30 minutes, there were obtained 42/60 mesh spherical fine granules.

EXAMPLE 13

By following the same procedure as described in Example 12 except that 10 g of synthetic aluminum silicate were used in place of 10 g of magnesium hydroxide, there were obtained 42/60 mesh spherical fine granules.

EXAMPLE 14

PS-310 (91 g) was melted by heating (90° C.), idebenone (9 g) was thrown thereinto, and the mixture was melted by stirring for 30 minutes maintaining the mixture at 90° C. By the same procedure as Example 1, 60/80 mesh of fine granules were obtained.

As a comparative experiment, hardened cotton seed oil (91 g) and idebenone (9 g) were processed in the same manner as above to obtain 42/62 mesh of fine granules.

The dissolution (%; hereinafter this means weight % unless specifically defined) of the drug from these fine granules stored at 40° C. are shown in Table 1.

TABLE 1

		Dissolution (%)					
	Hour	1	2	3	4	5	6
Fine granules made by using PS-310	Immediately after production	55.7	74.2	85.7	93.9	99.3	102.6
	After 1 month at 40° C.	60.8	73.3	82.2	88.6	92.9	96.5
	After 2 months at 40° C.	61.4	74.1	82.8	89.2	94.1	97.2
Fine granules made by using hardened cotton seed oil	Immediately after production	27.3	36.0	43.2	49.4	54.9	59.9
	After 1 month at 40° C.	33.0	44.0	53.0	61.0	68.0	74.0

From Table 1, the following facts are clarified:

The dissolution rate of idebenone from the fine granules obtained by using hardened cotton seed oil after 1 month storage at 40° C. is increased as compared with those obtained immediately after the production. To the contrary, the dissolution rate from the present fine granules using PS-310 shows a little change after 1 month storage and no change after 4 months storage; therefore, the release-sustaining ability of present fine granules is stable.

EXAMPLE 15

PS-310 (75g) and MS-310 (5g) were melted together by heating at 90° C., and then trepibutone (10g) and magnesium oxide (30g) were thrown thereinto and dispersed for 30 minutes maintaining the mixture at 80° C., followed by treating in the same manner as Example 1 to obtain 42/60 mesh of spherical fine granules.

The dissolution rates of the product in the mediums of I, II and pH 5 as described in J.P. 11 Ed. are shown in Table 2.

TABLE 2

	Dissolution (%)					
Hour	1	2	3	4	5	6
Medium I (pH 1.2)	19.4	29.4	37.1	43.8	50.0	54.7
pH 5.0	28.7	36.3	45.6	55.1	63.8	70.1
Medium II (pH 6.8)	29.5	37.6	45.5	52.9	60.7	66.8

From Table 2, it is apparent that the present fine granules exhibit almost the same rate of drug release in wide range of pH; therefore the fine granules have stable controlled release ability.

The dissolution rates of fine granules obtained in Example 15 in medium I and II after storage for 4 months at 40° C. are shown in Table 3.

TABLE 3

Hour	1	2	3	4	5	6
	Dissolution (%) in Medium I					
Immediately after production	19.4	29.4	37.1	43.8	50.0	54.7
After 4 months at 40° C.	18.9	30.0	38.1	44.2	49.2	53.7
	Dissolution (%) in Medium II					
Immediately after production	29.5	37.6	45.5	52.9	60.7	66.8
After 4 months at 40° C.	28.9	37.1	45.1	53.2	60.5	66.4

From Table 3, it is apparent that the release controlling ability of the present fine granules is extremely stable, because the dissolution rates after 4 months storage remain unchanged as compared with those taken immediately after the production.

EXAMPLE 16

PS-310 (75.2g) and MS-310 (20.8g) were melted together and 4g vinpocetine and Eudragit® L100-55 (Rohm Pharma. Co., West Germany) (60g) were put thereinto and dispersed by stirring for 30 minutes maintaining the mixture at 80° C., followed by treating in the same manner as Example 1 to obtain 42/60 mesh of spherical fine granules.

The dissolution rate of the product in mediums I and II after storage for 2 weeks and 4 months are shown in Table 4.

TABLE 4

Hour	Dissolution (%) 1	2	3	4	5	6
Medium I (pH 1.2)	43.4	63.2	75.1	83.5	89.8	95.1
Medium II (pH 6.8)	48.9	64.7	71.5	75.4	79.1	83.6

From Table 4, it is apparent that the present fine granules exhibit stable release controlling ability, because they release a drug at almost the same rate at under conditions having varied pHs.

EXAMPLE 17

PS-310 (75g) and MS-310 (21g) were melted together by heating at 90° C., and vinpocetine (4g) and Eudragit® L100-55 (produced by Rohm Pharma. Co., West Germany) (60g) were put thereinto and dispersed by stirring for 30 minutes maintaining the mixture at 80° C., followed by treating in the same manner as Example 1 to obtain 42/60 mesh of spherical fine granules. The dissolution rates of the product in mediums I and II after storage of 2 weeks and months at 40° C. are shown in Table 5.

TABLE 5

Hour	1	2	3	4	5	6
	Dissolution (%) in Medium I					
Immediately after production	36.5	56.4	69.0	77.5	84.4	89.8
After 2 weeks at 40° C.	41.6	61.4	73.1	81.5	87.9	92.6
After 4 months at 40° C.	52.5	66.5	81.0	87.0	91.6	96.4
	Dissolution (%) in Medium II					
Immediately after production	57.7	73.8	79.3	82.5	85.9	88.5
After 2 weeks at 40° C.	55.6	69.3	75.1	79.8	83.6	87.1
After 4 months at 40° C.	58.7	72.1	84.4	87.4	92.0	92.3

From Table 5, it is apparent that the present fine granules exhibit stable release-controlling ability which is unchanged after two weeks in comparison to those taken immediately after the production, and that the stability is unchanged after 4 months at 40° C.

EXAMPLE 18

PS-310 (75g) and MS-310 (25g) were melted together by heating at 90° C., and then AD-5467 (100g) was put thereinto and dispersed by stirring for 30 minutes maintaining the mixture at 90° C., followed by treating in the same manner as Example 1 to obtain 42/80 mesh of fine granules.

EXAMPLE 19

PS-310 (52g) and MS-310 (4g) were melted together by heating at 90° C., and AD-5467 (10g) and magnesium hydroxide (40g) were put thereinto and dispersed by stirring for 30 minutes maintaining the mixture at 90° C., followed by treating in the same manner as Example 1 to obtain 42/60 mesh of spherical fine granules. The dissolution rates of the product after storage at 40° C. are shown in Table 6.

TABLE 6

	Hour	Dissolution (%) 1	2	3	4	5	6
Medium I	Immediately after production	54.1	69.8	77.6	91.1	96.7	99.5
	After 1 month at 40° C.	48.1	60.1	76.1	88.1	96.3	99.3
Medium II	Immediate-after production	46.5	65.6	77.0	83.2	86.9	88.2
	After 1 month at 40° C.	47.3	70.5	80.7	86.1	86.4	86.4

From Table 6, it is apparent that the present fine granules exhibit stable release-controlling ability which is unchanged after 1 month in comparison to those taken immediately after the production.

EXAMPLE 20

PS-310 (192g) and MS-310 (32g) were melted together by heating at 90° C., and then AD-5467 (40g) and magnesium hydroxide (160g) were thrown thereinto and dispersed by stirring for 30 minutes maintaining the mixture at 90° C., followed by treating in the same manner as Example 1 to obtain 42/60 mesh of spherical fine granules.

Example 21	
AD-5467	40 g
PS-310	216 g
MS-310	8 g
Magnesium hydroxide	160 g

The above materials were treated in the same manner as Example 20 to obtain 60/80 mesh spherical fine granules.

The dissolution rates of the products obtained in Examples 20 and 21 in mediums I and II are shown in Table 7.

TABLE 7

	Hour	Dissolution (%) 1	2	3	4	5	6
Example 20	Medium I	66.5	89.3	97.5	100.0	100.0	100.0
	Medium II	76.7	88.5	90.5	90.3	90.6	90.8
Example 21	Medium I	36.6	50.0	58.8	65.9	71.7	76.3
	Medium II	36.8	48.4	71.8	78.5	81.8	82.5

As seen from Table 7, the present fine granules release AD-5467 at almost constant rate even in under conditions having varied pHs, and granules having fast dissolution rate (Example 20) or slow dissolution rate (Example 21) independent of pH can be produced by changing the ratio of fatty acid ester of polyglycerol in present matrixes.

Fine granule preparations containing AD-5467 obtained in Examples 20 and 21, and 4 mg/ml solution of AD-5467 in aqueous 5 W/V % suspension of gum arabic as a contrast were administered to each group of four rats (SD-rat, 8 weeks aged, male), respectively.

Each material was administered to fasted animals in a dose of 10 mg/Kg (body weight) of AD-5467 and concentrations in the blood were determined (Table 8).

TABLE 8

Hour	Concentration in blood (μg/ml) 0.25	0.5	1	1.5	2	3	5	7
Example 20	0.75	2.30	3.14	2.22	1.19	0.52	0.53	0.23
Example 21	0.16	0.73	0.88	1.12	1.23	0.79	0.57	0.69
Suspension in 5 w/v % aqueous gum arabic	5.97	2.85	1.38	0.70	0.41	0.20	0.20	0.13

Table 8 shows the following facts;

In the case of administering the aqueous suspension of gum arabic containing AD-5467, the concentration of AD-5467 in the blood reaches to the peak at 15 minutes and thereafter falls rapidly. To the contrary, present fine granules of Example 20 or 21 exhibit the peak after 1 hour or 2 hours, respectively. Therefore, present fine granules have excellent release-controlling ability.

EXAMPLE 22

Stearyl mono(deca)glyceride (produced by Sakamoto Yakuhin Co.) (92g) was melted by heating at 90° C., and ipriflavone (18g) was put thereinto and dispersed by stirring for 30 minutes maintaining the mixture at 90° C., followed by treating in the same manner as Example 1 to obtain 42/60 mesh of spherical fine granules.

The fine granules were administered orally to four beagles (aged 1 year, about 10 Kg) each in a dose containing 200 mg of ipriflavone, and the concentration of 7-hydroxy-3-phenyl-4H-1-benzopyran-4-one (main metabolite of ipriflavone) in the blood was determined. The results are shown in Table 9. As the contrast, the dispersion of 200 mg of ipriflavone in 5 W/V % aqueous gum arabic suspension (hereinafter abbreviated as "suspension") was employed.

TABLE 9

Hour	Concentration in blood (μg/ml) 0.25	0.5	1	1.5	2	3	5	7
Example 22	43.1	120.7	198	187.1	209.2	219.5	125.7	121.7
Suspension	0.1	7.2	10.3	21.9	33.0	25.0	32.1	25.6

As seen from Table 9, the absorption of ipriflavone from present fine granules obtained in Example 22 amounts to 10 times higher and sustains longer as compared with "suspension".

EXAMPLE 23

(1) PS-310 (860g) and MS-310 (100g) were melted together by heating at 90° C., and 90 g of phenylpropanolamine was thrown thereinto and dispersed by stirring for 30 minutes maintaining the mixture at 90° C., followed by treating in the same manner as Example 1 to obtain 30/42 mesh of spherical fine granules.

(2) The fine granules (300g) obtained in the above (1) were loaded into a fluid-bed drier (FD-3S; Fuji Sangyo Co., Japan) and sprayed with 5 W/V % aqueous solution of hydroxypropylmethylcellulose (TC-5R; Shinetsu Chemical Co., Japan), controlling the temperature of inlet air at 45° C. and that of granules at 35° C.; thereby coated fine granules were obtained.

The dissolution rates of phenylpropanolamine in water from the fine granules obtained in Example 23 (1) and (2) are shown in Table 10.

TABLE 10

Hour	Dissolution 1	2	3	4
Example 23(1); fine granules	22.9	31.3	37.8	38.6
Example 23(2); coated fine granules	18.8	27.0	33.5	34.9

As seen from Table 10, present fine granules exhibit almost unchanged elution rate after and before coating and have stable release-controlling ability.

EXAMPLE 24

(1) PS-310 (800g) and MS-310 (100g) were melted together by heating at 90° C., and then caffeine (100g) was thrown thereinto and dispersed by stirring for 30 minutes maintaining the mixture at 90° C., followed by treating in the same manner as Example 1 to obtain 42/60 mesh of spherical fine granules.

(2) The fine granules (250g) obtained in the above (1) were loaded into a fluid-bed drier (FD-3S; Fuji Sangyo Co., Japan) and sprayed with 5 W/V % solution of hydroxypropylmethylcellulose in ethanol, controlling the inhalant air at 45° C. and the granules at 35° C.; thereby coated fine granules were obtained.

EXAMPLE 25

The fine granules (100g) obtained in Example 24 (1), Avicel® (90g), sodium carboxymethylcellulose (Ac-Di-Sol; FMC-Asahi Kasei Kogyo Co., Japan) (10g) and magnesium stearate (0.6g) were mixed and tabletted with a pounder (plain) of 10 mm in diameter at 0.2 ton/cm^2 to obtain tablets.

The dissolution rates of caffeine from the fine granules obtained in Example 24 and the tablets obtained in Example 25 are shown in Table 11.

TABLE 11

Hour	Dissolution (%)					
	1	2	3	4	5	6
Fine granules	16.1	24.5	33.4	38.3	43.8	46.5
Tablets from coated fine granules	17.2	27.8	36.7	45.5	48.9	51.4

As seen from Table 11, caffeine release from the tablets produced by tabletting coated fine granules (Example 25) occurs at the same rate as from the coated fine granules not being compressed to tablets (Example 24), and both preparations exhibit stable release-controlling ability.

EXAMPLE 26

PS-310 (64g) and MS-310 (16g) were melted together by heating at 90° C., and 20 g of delapril was thrown thereinto and dispersed by stirring for 30 minutes maintaining the mixture at 70° C., followed by treating in the same manner as Example 1 to obtain 60/80 mesh of spherical fine granules. The dissolution rates of delapril from the fine granules are shown in Table 13.

TABLE 13

Hour	Dissolution (%)					
	1	2	3	4	5	6
60/80 mesh fine granules	48.3	74.1	85.5	90.1	92.3	93.0

The fine granules obtained in the above procedure were administered to a rat under fast overnight in a dose of 20 mg/Kg as delapril and the concentration of (N-[N-[(S)-1-carboxy-3-phenylpropyl]-L-alanyl]-N-indan-2-yl) glycine (metabolite of delapril hydrochloride) in the blood was determined and shown in Table 14. As a contrast, a solution oft delapril hydrochloride (4mg/ml) in 5 W/V % aqueous suspension of gum arabic was used.

TABLE 14

Hour	Concentration in blood (μg/ml)							
	0.25	0.5	1	1.5	2	3	5	7
60/80 mesh fine granules	0.881	0.816	0.785	0.647	1.07	0.387	0.115	0.052
Suspension of delapril hydrochloride in 5 w/v % aqueous gum arabic	5.46	4.63	0.875	0.427	0.221	0.200	0.090	0.007

As seen from Table 14, in the case of administering the solution of delapril hydrochloride, rapid disappearance of concentration in the blood is observed, but the present fine granules exhibit sustained concentration in the blood corresponding to the dissolution rate. See Table 13 for the dissolution rates of the 60/80 mesh fine granules.

EXAMPLE 27

MS-310 (8g), PS-310 (32g) and stearyl tri(mono)-glyceride (TS-310; produced by Sakamoto Yakuhin Co., Japan) (40g) were melted together by heating and the temperature of the mixture was adjusted to 70° C., and then 20 g of delapril was thrown thereinto and dispersed by stirring for 30 minutes, followed by treating in the same manner as Example 1 to obtain 42/60 mesh of fine granules.

EXAMPLE 28

The fine granules (250g) obtained in Example 27 were loaded into a fluid-bed drier (FD-35; Fuji Sangyo Co., Japan) and sprayed with 5 W/W % solution of hydroxypropylcellulose in ethanol for coating, controlling the inhalant air at 45° C. and granules at 35° C.; thereby coated fine granules were obtained.

EXAMPLE 29

The coated fine granules (100g) obtained in Example 28, Avicel® (90g), sodium carboxymethylcellulose (Ac-Di-Sol; FMC-Asahi Kasei Kogyo Co.,Japan) (10g) and magnesium stearate (0.6g) were mixed and tabletted with a punch (plain) of 10 mm in diameter at the pressure of 0.2 ton/cm^2 to obtain tablets.

The dissolution rates of delapril hydrochloride from the fine granules, coated granules or tablets of Examples 27, 28 and 29 are shown in Table 15.

TABLE 15

Hour	Dissolution (%)					
	1	2	3	4	5	6
Example 27	56.9	83.3	89.8	89.9	89.2	90.6
Example 28	51.5	78.4	89.2	92.6	93.1	92.5
Example 29	62.9	85.9	89.5	91.0	91.9	92.5

As seen from Table 15, the release of delapril hydrochloride from present coated fine granules (Example 28) or tablets obtained by tabletting the coated fine granules (Example 29) is unchanged as compared with the fine granules before coating (Example 27), and all of them exhibit stable and sustained dissolution.

EXAMPLE 30

PS-310 (65.6g) and MS-310 (9.4g) were melted together at 90° C., and delapril hydrochloride (25 g) was thrown thereinto and dispersed by stirring for 30 minutes maintaining the mixture at 70° C., followed by treating in the same manner as Example 1 to obtain 42/60 mesh of spherical fine granules.

The release of delapril hydrochloride from the fine granules when they were stored at 40° C. is shown in Table 16.

TABLE 16

Hour	Dissolution (%)					
	1	2	3	4	5	6
Immediately after production	38.4	57.1	74.3	83.2	85.7	86.8
After 10 days at 40° C.	38.9	58.8	73.2	80.7	83.8	84.1
After 3.5 months at 40° C.	35.8	53.2	66.2	74.5	79.0	81.7

As seen form Table 16, the present fine granules have excellent release-controlling ability even after a long period of Storage, which proves that they are extremely stable controlled release preparation.

EXAMPLE 31

The fine granules obtained in Example 17 were filled into capsule No. 1 of J.P. 11 Ed. to obtain a capsule preparation.

EXAMPLE 32

The fine granules obtained in Example 18 were tabletted with a punch (plain) of 6 mm in diameter at the pressure of 0.1 ton/cm^2 to obtain tablets.

EXAMPLE 33

In the same manner as Example 24 (1) with a 900 rpm rotation number of the disk, employing PS-310 (800g), MS-310 (100g) and caffeine (100g), 12/48 mesh of granules were obtained.

We claim:

1. Fine granules or granules which comprise a pharmaceutically active acidic ingredient and a water-insoluble or slightly water-soluble solid base having a particle size of not more than 50 μm in a proportion of 1 to 80 weight %, dispersed into a matrix, wherein said matrix is solid at ambient temperature and contains a fatty acid ester of polyglycerol, said active acidic ingredient being contained in a proportion of 0.005 to 75 weight % said fine granules being composed of not less than 75 weight % of particles of 500 to 10 μm, not more than 5 weight % of particles of not less than 500 μm and not more than 10 weight % of particles of not more than 10 μm and said granules being composed of not less than 90 weight % of particles of 1410 to 500 μm and not more than 5 weight % of particles of not more than 177 μm.

2. Fine granules or granules according to claim 1 which are coated with a coating agent.

3. A capsule which comprises the fine granules or granules of claim 2 filled therein.

4. A tablet which is produced by tabletting the fine granules or granules of claim 2.

5. A capsule which comprises the fine granules or granules according to claim 1 filled therein.

6. A tablet which is produced by tabletting the fine granules or granules according to claim 1.

7. A tablet according to claim 6, wherein a disintegrating agent is contained.

8. Fine granules or granules according to claim 1, wherein the amount of the fatty acid ester of polyglycerol in the matrix is about 0.001 to 50 times the weight of the pharmaceutically active acidic ingredient.

9. Fine granules or granules which comprise a pharmaceutically active basic ingredient and an enteric substance having a particle size of not more than 50 μm in a proportion of 1 to 80 weight % dispersed into a matrix, wherein said matrix is solid at ambient temperature and contains a fatty acid ester of a polyglycerol, said active basic ingredient contained in a proportion of 0,005 to 75 weight %, said fine granules being composed of not less than 75 weight % of particles of 500 to 10 μm, not more than 5 weight % of particles of not less than 500 μm and not more than 10 weight % of particles of not more than 10 μm and said granules being composed of not less than 90 weight % of particles of 1410 to 500 μm and not more than 5 weight % of particles of not more than 177 μm.

10. Fine granules or granules according to claim 9, which are coated with a coating agent.

11. A capsule which comprises the fine granules or granules of claim 9 filled therein.

12. A tablet which is produced by tabletting the fine granules or granules of claim 9.

13. A tablet which is produced by tabletting fine granules or granules which comprise a pharmaceutically active ingredient dispersed into a matrix which is solid at ambient temperature and contains a fatty acid ester of a polyglycerol, the ester being present throughout the fine granules or granules, said fine granules being composed of not less than 75 weight % of particles of 500 to 10 μm, not more than 5 weight % of particles of not less than 500 μm and not more than 10 weight % of particles of not more than 10 μm and said granules being composed of not less than 90 weight % of particles of 1410 to 500 μm and not more than 5 weight of particles of not more than 177 μm.

14. A tablet according to claim 13, which contains a disintegrating agent.

15. A tablet which is produced by tabletting fine granules or granules which comprise a pharmaceutically active ingredient dispersed into a matrix which is solid at ambient temperature and contains a fatty acid ester of a polyglycerol, the ester being present throughout the fine granules or granules, said fine granules being composed of not less than 75 weight % of particles of 500 to 10 μm, not more than 5 weight % of particles of not less than 500 μm and not more than 10 weight % of particles of not more than 10 μm and said granules being composed of not less than 90 weight % of particles of 1410 to 500 μm and not more than 5 weight % of particles of not more than 177 μm, wherein the fine granules or granules are coated with a coating agent.

16. A tablet according to claim 15, which contains a disintegrating agent.

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Divisional Application of USP 5,399,35[illegible]

US005593690A

United States Patent [19]

Akiyama et al.

[11] **Patent Number: 5,593,690**

[45] **Date of Patent: *Jan. 14, 1997**

[54] **SUSTAINED RELEASE PREPARATIONS**

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[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. No. 5,399,357.

[21] Appl. No.: **388,520**

[22] Filed: **Feb. 14, 1995**

Related U.S. Application Data

[62] Division of Ser. No. 807,630, Dec. 13, 1991, Pat. No. 5,399,357, which is a continuation of Ser. No. 433,223, Nov. 8, 1989.

[30] **Foreign Application Priority Data**

Nov. 8, 1988	[JP]	Japan	63-282994
Nov. 21, 1988	[JP]	Japan	63-294379
Oct. 3, 1989	[JP]	Japan	1-259674

[51] **Int. Cl.**^{6} **A61K 9/16**; A61K 9/26; A61K 9/50; A61K 47/34

[52] **U.S. Cl.** **424/457**; 424/486; 424/458; 424/459; 424/461; 424/462; 424/470; 424/490; 424/494; 424/495; 424/497; 424/501; 514/785; 514/951; 514/963; 514/965

[58] **Field of Search** 424/457, 486, 424/458–459, 461–462, 420, 490, 494–495, 497, 501; 514/785, 951, 963, 965

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[57] **ABSTRACT**

There is provided a matrix preparation produced by dispersing a pharmaceutically active ingredient into a matrix which is solid at ambient temperature and comprised of a fatty acid ester of a polyglycerol. The preparation has stable release-controlling ability, can be processed to fine granules, granules, capsules, tablets etc., and contributes to reduce the administration times of the active ingredient and side effects of the ingredient.

7 Claims, No Drawings

SUSTAINED RELEASE PREPARATIONS

This application is a division, of application Ser. No. 07/807,630, filed Dec. 13, 1991 (U.S. Pat. No. 5,399,357) which is a continuation of Ser. No. 07/433,223, filed Nov. 8, 1989, abandoned.

Present invention relates to stable, controlled release matrix preparations.

For the purposes of reducing a number of doses under sustaining the effect of a drug, and suppressing rapid elevation of drug concentration in blood to thereby alleviate side-effects or retaining drug concentration in blood for a long time, controlled release preparations, particularly sustained release pharmaceutical preparations have been studied with a variety of drug substances and by means of a number of methods. The controlled release preparations include, for example, capsule-type dosage forms comprising a drug-containing core portion covered with a membrane and matrix-type dosage forms consisting of a drug dispersed in the drug-release controlling layer.

These conventional controlled release preparations, which are required to be subjected to more sophisticated processing techniques, have been provided in the forms of tablets, capsules or granules.

Taking into consideration the fact that a recently increasing number of aged persons and children are given medicine, however, controlled release preparations in the form of fine granules are regarded desirable. In addition, one of the advantages that fine granules can offer lies in that their doses can be easily adjusted. However, stable controlled release preparations, particularly fine granules have not been obtainable, as far as they are produced in accordance with a production process for conventional controlled release preparations. Therefore, no controlled release fine granules has been commercialized so far in the past.

Under these circumstances, the present inventors conducted extensive investigation into controlled release matrix preparations which can be prepared by means of a practical and economical production method without the use of a solvent harmful to human beings, can also be easily adjusted in dissolution rate, is easy for patients to take and stable. As a result, present inventors found that when an active ingredient is dispersed into a matrix being solid at ambient temperature (15° to 35° C.) and consisting of or containing a fatty acid ester of a polyglycerol, which has not been employed in conventional matrix preparations, to produce a matrix preparation, particularly fine granules, an ideal controlled release matrix preparation can be obtained unexpectedly. The matrix preparation thus obtained excels remarkably in not only stability and release-controlling ability but also economy, toxicity, effect, etc. and furthermore that when an pharmaceutically active acidic ingredient and a solid base being insoluble or slightly soluble in water, or an active basic ingredient and an enteric substance, are dispersed during the production process for the matrix preparation as described above, there can be obtained a controlled release fine granules being provided with pH-independence, which allows an active ingredient to dissolve in the stomach and intestine at a constant rate. In addition to the above excellent characteristics, the resultant matrix preparations are suited for commercialization. The fine granules described here is named as Micromatrix system (MMS).

These findings have led the inventors to the completion of this invention.

Thus, this invention relates to:

1. A matrix preparation which comprises a pharmaceutically active ingredient dispersed into a matrix being solid at ambient temperature and consisting of a fatty acid ester of a polyglycerol or containing the same.

2. Fine granules or granules which comprise a pharmaceutically active ingredient dispersed into a matrix being solid at ambient temperature and consisting of a fatty acid ester of a polyglycerol or containing the same.

3. A matrix preparation according to the item 1, wherein microcrystalline wax is contained in the matrix.

4. Fine granules or granules according to the item 2, wherein microcrystalline wax is contained in the matrix.

5. Fine granules or granules according to the item 2 or 4, wherein the fine granules or granules are coated with a coating agent.

6. Capsules wherein the fine granules or granules according, to the item 2 or 5 are filled.

7. Tablets which are produced by tableting the fine granules or granules according to the item 2 or 5.

8. Tablets according to the item 7, which contains a disintegrating agent.

9. Fine granules or granules which comprise a pharmaceutically active acidic ingredient and a water-insoluble or slightly water-soluble solid base dispersed into a matrix being solid at ambient temperature and consisting of a fatty acid ester of a polyglycerol or containing the same.

10. Fine granules or granules which comprise a pharmaceutically active basic ingredient and an enteric substance dispersed into a matrix being solid at ambient temperature and consisting of fatty acid ester of a polyglycerol or containing the same.

11. Fine granules or granules according to the item 9 or 10, which are coated with a coating agent.

12. Capsules wherein the fine granules or granules according to the item 9, 10 or 11 are filled.

13. Tablets which are produced by tableting the fine granules or granules according to the item 9, 10 or 11.

14. Tablets according to the item 13, wherein a disintegrating agent is contained.

The fatty acid ester of a polyglycerol in this invention is an ester formed by the combination of polyglycerol with a fatty acid. Polyglycerol is "a polyhydric alcohol having n (in a cyclic polyglycerin)–n+2 (in a straight or branched polyglycerin) hydroxyl groups and n–1 (in a straight or branched polyglycerin)–n (in a cyclic polyglycerin) ether combinations in one molecule" (Polyglycerin esters, p. 12, May 20, 1986, edited by Sakamoto Yakuhin Kogyo Co., Ltd., Japan). As the polyglycerol, there can be used, for example, those represented by the formula:

$$HO\!\left(CH_2-\underset{\displaystyle OH}{\underset{|}{CH}}-CH_2-O\right)_{n}\!H \qquad [I]$$

(wherein n is a degree of polymerization). Normally, n is an integer of 2 to 50, preferably 2 to 20 more preferably 2 to 10. As specific examples of such polyglycerols, there are used, for example, diglycerol, triglycerol, tetraglycerol, pentaglycerol, hexaglycerol, heptaglycerol, octaglycerol, nonaglycerol, decaglycerol, pentadecaglycerol, eicosaglycerol and triacontaglycerol, and among others, frequent use is made of tetraglycerol, hexaglycerol and decaglycerol. As the fatty acid, there can be used, for example, saturated or unsaturated higher fatty acids having a number of carbon atoms of 8 to 40, preferably 12 to 22. As the fatty acids, there are used, for example, palmitic acid, stearic acid, oleic acid, linolic acid, linoleic acid, myristic acid, lauric acid, ricinoleic acid, caprylic acid, capric acid and behenic acid, and among others, frequent use is made of stearic acid, oleic acid, lauric acid, ricinoleic acid, and the like. As the fatty acid esters of polyglycerols, there are used monoesters or polyesters from the polyglycerols and fatty acids as mentioned above. Such fatty acid esters of polyglycerols have ordinarily a molecular

weight of 200 to 5000, preferably 300 to 2000, and an HLB (hydrophilic-lipophilic balance) of 1 to 22, preferably 1 to 15. Also, the fatty acid esters of polyglycerols can suitably be selected depending upon the type of active ingredients utilized, and there may be used, for example, those being capable of melting by warming active ingredients in proportions of 0.00001 to 5 g/ml, preferably 0.0001 to 1 g/ml. As specific examples of the fatty acid esters of polyglycerols, there may be used, for example, caprylyl di(tri)glyceride, capryl di(tri)glyceride, caprylyl mono(deca)glycerida, lauryl mono(deca)glyceride, lauryl mono(hexa)glyceride, lauryl mono(tetra)glyceride, oleyl di(tri)glyceride, oleyl di(tetra)glyceride, linolyl di(tri)glyceride, linolyl di(tetra)glyceride, linolyl di(hexa)glyceride, linolyl di(hepta)glyceride, stearyl mono(deca)glyceride, stearyl deca(deca)glyceride, stearyl mono(tetra)glyceride, stearyl mono(tetra)glyceride, stearyl mono(hexa)glyceride, stearyl sesqui(hexa)glyceride, oleyl sesqui(deca)glyceride, oleyl penta(hexa)glyceride, stearyl tri(hexa)glyceride, stearyl penta(hexa)glyceride, oleyl mono(hexa)glyceride, lauryl mono(deca)glyceride, stearyl tri(tetra)glyceride, stearyl penta(tetra)glyceride, oleyl mono(tetra)glyceride, oleyl penta(tetra)glyceride, lauryl mono(tetra)glyceride, palmityl mono(deca)glyceride, palmityl deca(deca)glyceride, palmityl mono(hexa)glyceride, palmityl sesqui(hexa)glyceride, palmityl tri(hexa)glyceride, palmityl penta(hexa)glyceride, palmityl mono(tetra)glyceride, palmityl tri(tetra)glyceride, palmityl penta(tetra)glyceride, and the like, either solely or in mixtures of more than two kinds thereof, and among others, frequent use is made for example of stearyl penta(tetra)glyceride (e.g., PS-310 produced by Sakamoto Yakuhin Co. of Japan), stearyl mono(tetra)glyceride (e.g., MS-310 produced by Sakamoto Yakuhin Co., Japan), stearyl penta(hexa)glyceride (e.g., PS-500 produced by Sakamoto Yakuhin Co., Japan) and stearyl sesqui(hexa)glyceride (e.g., SS-500 produced by Sakamoto Yakuhin Co. of Japan), stearyl mono(deca)glyceride, and the like. Particularly, in the case of the fatty acid ester of a polyglycerol is stearyl mono(deca) glyceride, excellent absorption of pharmaceutical active ingredient and stable controlled release ability are attained. These fatty acid esters of polyglycerols are used in such quantities as may correspond to about 0.001 to 50 times the weight of the active ingredient, preferably 0.005 to 5 times, however, the dose is not limited as far as the object of the invention is achieved.

In this invention matrixes containing fatty acid esters of polyglycerols are in the solid form at ambient temperature. The matrixes may best be incorporated with the fatty acid esters of polyglycerols as described above in such quantities as mentioned previously. As the matrix employable in this invention, there are used matrixes which are in the solid form at ambient temperature and have low melting points (30° to 150° C., preferably 40° to 120° C.). These matrixes can be incorporated, for example, with lipids in addition to the fatty acid esters of polyglycerols to thereby produce more preferred results. As these lipids, there are used pharmaceutically acceptable, water-insoluble lipids which demonstrate an action to regulate a dissolution rate of drugs, preferably lipids having a softening point or melting point of 40° to 120° C., preferably 40° to 90° C. As specific examples of these lipids, there are used for example hydrogenated oils (e.g., castor oil, cotton seed oil, soybean oil, rapeseed oil, beef tallow, and the like), beeswax, carnauba wax, spermaceti paraffin, lecitin, microcrystalline wax, fatty acids such as stearic acid and palmitic acid, or their salts (e.g., sodium salts, potassium salts, and the like), aliphatic alcohols such as stearyl alcohol and cetyl alcohol, and glycerides, among others. Frequent use is made for example of hardened cotton seed oil, hardened castor oil, hardened soybean oil, carnauba wax, stearic acid, stearyl alcohol and microcrystalline wax. The lipids may be used in an amount not hindering the object of the invention and normally they are used in such quantities as may correspond to about 0.01 to 100 times the weight of the active ingredient, preferably 1 to 20 times.

The matrixes being solid at ambient temperature usable in this invention can suitably be incorporated with additives being generally employable in the production of fine granules or granules, unless there is particular hindrance. For example, there can suitably be used excipients, such as lactose, corn starch, Avicel®, powdered sugar and magnesium stearate; binding agents, such as starch, sucrose, gelatin, powdered gum arabic, methylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose and polyvinylpyrrolidone; disintegrating agents, such as calcium carboxymethylcellulose and substituted hydroxypropylcellulose; and other additives, such as coloring agents, flavoring agents, adsorbents, preservatives, wetting agents, antistatic agents and disintegration prolonging agents.

As the parmaceutically active ingredient, there may be employed drugs having relatively higher melting points (not lower than 121° C.), such as phenylpropanolamine hydrochloride, chlorphenylamine maleate, phenylepherin hydrochloride, theophylline, caffeine, procaineamide hydrochloride, sulfanylamide, cephalexin, ampicillin, molsidomine, indomethacin, sulfisoxazole, sulfadiazine, diazepam, valproic acid, quinidine sulfate, asprin and 3,4-dihydro-2,8-diisopropyl-3-thioxo-2H-1,4-benzoxadine-4-acetic acid (hereinafter referred to as "AD-5467"), delapril hydrochloride, ipriflavone, trepibutone and the like; drugs having relatively lower melting points (about 0° to 120° C., preferably e.g. 40° to 120° C.), such as isosorbide nitrate, ketoprofen, cyclanderate, idebenone and 2-(12-hydroxydodeca-5,10-dinyl)-3,5,6-trimethyl-1,4-benzoquinone (hereinafter referred to as "AA-861"), and peptides or proteins such as insulin, vasoopressin, interferon, IL-2, urokinase, a.FGF (acidic fibroblast growth factor), b.FGF (basic fibroblast growth factor), etc. The matrix preparation of present invention can permit these drugs to gradually dissolve or/and be absorbed in the digestive tracts.

The solubilty and absorption from gastrointestinal tract of active ingrectients vary with physicochemical properties. Generally speaking, base active ingredients, which show an increased solubility in the acid pH range but a decreased solubility in the alkali pH range, dissolve rapidly in the stomach that they pass through under the influence of acid gastric juice, but dissolve slowly in the neutral to weakly alkaline intestine. On the other hand, acid active ingredients, which exhibit an enhanced solubility in the alkaline pH region but a lower solubility in the acid pH region, dissolve rapidly in the neutral to weakly alkaline intestine but dissolve slowly in the stomach that they pass through under the influence of acid gastric juice. Accordingly, in order to retain the appropriate release-controlled dissolution of the active ingredient in the pH-independent manner so that its dissolution may be realized at a constant rate in both the stomach and intestine, in this invention, the acid active ingredient and water-insoluble or slightly water-soluble solid base, or the base active ingredient and enteric substance, are dispersed into the matrix of the fatty acid ester of a polyglycerol or the matrix containing the same which is in the solid form at ambient temperature.

The acid active ingredient as mentioned herein is that of which aqueous solutions present acidity (e.g. pH of not less

than 1.5 but less than 7.0, preferably 2.0 to 6.8), or that which has acid group(s) (e.g. carboxyl group etc.). As the ingredient, there may be used, for example, indomethacin, salicylic acid, AD-5467, trepibutone, aspirin, valproic acid, ketoprofen, ibuprofen, epinephrine, haloperidol, reserpine, ascorbic acid, acetaminophen and probenecide and AD-5467; trepiptone, indomethacin, and the like are among others preferably used. The solid base used includes water-insoluble or slightly water-soluble (solubility in water at 37° C. of not more than 0.1 g/ml, preferably not more than 0.001 g/ml) solid bases, whereupon the less soluble ones can produce more desirable results. As these solid bases, there are used oxides, hydroxides, inorganic acid salts or organic acid salts of metals of Groups I, II and III in the periodic table, either solely or in mixtures of not less than two kinds thereof, such as magnesium oxide, magnesium hydroxide, magnesium silicate, magnesium carbonate, aluminum silicate, aluminum hydroxide, silicic acid (cyloid, aerosol), magnesium aluminometasilicate (neusiline), magnesium stearate, aluminum stearate and sodium stearate. The solid bases have normally a particle size of not more than 50 μm, preferably 0.05 to 20 μm, while they are used in the proportions of usually 1 to 80 weight %, preferably 1 to 50 weight %, more preferably 10 to 30 weight %, to the total amount.

The basic active ingredient is that of which aqueous solutions present alkalinity (pH 7.0 to 13.0, preferably 7.0 to 10.5), or that which has basic group(s) (e.g. amino group etc.). As the ingredient, there are used, for example, vinpocetine, estazolam, acetazolamide, papaverine, tolbutamide, acetohexamide, theophylline, verapamil, quinidine, propranolol, morphine, ephedrine, scopolamine, chlorpromazine, manidipin hydrochloride, and the like with vinpocetine, acetazolamide, etc. being among others frequently used. As the enteric substance, there are used substances which hardly dissolve in the stomach but start to dissolve in the intestine, whereby finely powdered (10 to 0.05 μm) substances as used can particularly produce desired results. Such enteric substances may be acidic compounds of high-molecular (molecular weights ranging from 30,000 to 500,000, preferably from 70,000 to 400,000), and there are used, for example, hydroxypropylmethylcellulose phthalate, cellulose acetate phthalate, carboxymethylethylcellulose (CMEC AQ®; produced by Kojin Co., Japan), methacrylic acid/methyl methacrylate copolymers (Eudragit® L100-55, Eudragit L-100, Eudragit S-100; produced by Rohm Pharma Co., West Germany) and the like, either solely or in mixtures of not less than two kinds of these acidic high molecular weight compounds. Particularly, Eudragit L100-55, etc. are frequently used. The enteric substances normally show a particle size of not more than 50 μm, preferably 0.05 to 10 μm, while they are used in proportions of usually 1 to 80 weight %, preferably 1 to 50 weight %, more preferably 10 to 30 weight %, to the total weight.

The active ingredients inclusive of the above-mentioned acid and basic active ingredients are contained in the matrix preparation of this invention in the proportions of 0.005 to 75 weight %, preferably 0.01 to 50 weight %, to the total weight of the fine granules.

The matrix preparation of this invention can be produced by dispersing (the term "disperse" includes the dispersion of not only solid but also liquid substances) an active ingredient into a matrix of a fatty acid ester of a polyglycerol or a matrix containing the same which is in the solid form at ambient temperature, followed by bringing to fine granules or granules; dispersing an acid active ingredient and a water-insoluble or slightly water-soluble solid base into a matrix of a fatty acid ester of a polyglycerol or a matrix containing the same which is in the solid-form at ambient temperature, followed by bringing to fine granules or granules; or dispersing a basic active ingredient and an enteric substance into a matrix of a fatty acid ester of a polyglycerol or a matrix containing the same which is in the solid form at ambient temperature, followed by bringing to fine granules or granules. Thus, the stable, controlled release matrix preparations, particularly fine granules or granules of present invention can be obtained for example by melting by warming (40° to 150° C. preferably 50° to 110° C.) a fatty acid ester of a polyglycerol alone or in conjunction with the above-mentioned additives being capable of forming with it a matrix being solid at ambient temperature, adding to the melted substance an active ingredient, an acid active ingredient and a water-insoluble or slightly water-soluble solid base or a basic active ingredient and an enteric substance in suitable amounts to produce a dispersion, followed by cooling and bringing to a matrix, particularly fine granules or granules. On the occasion when the fatty acid ester of a polyglycerol is melted by warming, the above-described lipid and additives may be melted by warming together with it or may be melted individually and then mixed with it. In addition, the active ingredient as well as particles of the additives can be added simultaneously. A known granulator can be employed to produce the objective matrix, such as fine granules (normally composed of not less than 75 weight % of particles of 500 to 10 μm, not more than 5 weight % of particles of not less than 500 μm and not more than 10 weight % of particles of not more than 10 μm; particularly not less than 75 weight % of particles of 500 to 105 μm, not more than 5 weight % of particles of not less than 500 μm and not more than 10 weight % of particles of not more than 74 μm), granules (composed of, for example, not less than 90 weight % of particles of 1410 to 500 μm and not more than 5 weight % of particles of not more than 177 μm) and the like.

Granulation under cooling is particularly preferred for producing fine granules, and for example, it is desirable to produce spherical fine granules through spray cooling, in particular through spray-chilling. Spray chilling can be performed for example by dripping or adding dropwise the melted material at a constant rate (2 to 200 g/min., preferably 5 to 100 g/min.) onto a high-speed rotating disc (e.g., a smooth or flat disc, such as a disc made of aluminum, having 5 to 100 cm in diameter, preferably 10 to 20 cm) at a rotation number of usually 10 to 6,000 rpm, preferably 900 to 6,000 rpm, more preferably 1,000 to 3,000 rpm.

Present matrix preparations, particularly fine granules or granules may be those coated with a coating agent by a per se known method for reforming their surfaces, masking their taste or giving them a solubility in the intestine etc. As the coating agent, there are used, for example, hydroxypropylmethylcellulose, ethylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, sugar powder, polyoxyethylene glycol, Tween 80, Pluronic F 68, castor oil, cellulose acetate phthalate, hydroxypropylmethylcellulose acetate succinate, acrylic acid polymer (e.g. Eudragit® L100-55, L-100, S-100, produced by Rohm Pharma co., West Germany), carboxymethylcellulose, polyvinylacetyl, diethylaminoacetate, waxes, and the like, as well as pigments, such as talc, titanium oxide, red etc. These agents may be used solely or in combination with two kinds or more to make one or two layers of coating. For the coating, there can be employed per se known method. Namely, the coating may be carried out by, for example, spraying a liquid made by dispersing or dissolving the coating agent in water or an organic solvent

on a matrix by pan-coating, fluidized-coating or centrifugal fluidized coating.

The coating of fine granules is preferably carried out at a temperature of 25° to 70° C., preferably 25° to 40° C.

The controlled release matrix preparations preferably take the form of fine granules or granules but in cases where persons involved in the medical service or patients ask for tablets for the purpose of convenience, the matrix, preferably the fine granules or granules as obtained by the above procedure can be compressed to tablets, together with excipients (among others, disintegrating agent, etc. as mentioned above) added, if necessary, in accordance with the conventional method at a pressure of, for example, 0.2 to 2.0 ton/cm^2, preferably 0.2 to 1.0 ton/cm^2. Furthermore, the fine granules or granules can be filled into capsules by a conventional manner to process to capsule preparations. These tablets or capsules have excellent effects and stable release rate equal to the present matrix preparations, particularly fine granules or granules; however, it is to be understood that such tablets and capsules are included in the scope of present invention.

The present matrix preparations of fine granules, granules, tablets, capsules etc. obtained by the above procedures can be put into use in the same manner as the conventional fine granules, granules, tablets, capsules, and the like, for example, by administering them orally to subjects (mammals, such as human beings, domestic animals and experimental animals) to whom the active ingredient is intended for used.

The present matrix preparations of fine granules, granules, tablets and capsules possess the extremely stable controlled release ability being free from variation in drug (active ingredient) release rate and hardly show any change in the drug release pattern even after storage for a prolonged period of time, and further a bad taste or odor of a drug can be masked in the preparation. Moreover, the present preparations are easy to control the drug release rate, are applicable to a wide range of drugs, do not require the use of organic solvent in the production process, do not cause air pollution in the production steps, do not provide any risk of solvent remaining in the pharmaceutical preparations nor produce any static electric charge and can be produced by the simplified production process requiring no special equipment, and consequently can be said to be the ideal controlled release preparations.

Described in the following are the examples to illustrate this invention in more particularly, but this invention is understood to not be limited to such examples.

In the following examples, the dissolution rate was determined by the method referred below:

According to Method 2 (paddle method) of "The Method for Determining Dissolution" in Japanese Pharmacopoeia, 11th Edition (herein after referred as "J.P. 11 Ed."), the dissolution from a test material was carried in 900 ml of dissolution medium containing a surfactant under 100 rpm of revolution; sampling of the medium was carried periodically, and the dissolution rates were calculated on the UV-absorbance of each filtrate of the samples.

EXAMPLE 1

A 80 g quantity of stearyl penta(tetra)glyceride (PS-310® produced by Sakamoto Yakuhin Co., Japan; hereinafter referred to as PS-310) was warmed and melted at 90° C., and 20 g of theophylline was put into the molten material, followed by stirring for 30 minutes to achieve dispersion. The dispersion was warmed at 90° C. and dripped at a rate of 20 g/min. onto an aluminum-made disc of 15 cm in diameter revolving at 2000 rpm. to produce spherical fine granules which passed through a 42 mesh sieve but did not pass through a 60 mesh sieve (hereinafter described briefly as "42/60 mesh").

EXAMPLE 2

By following the same procedure as described in Example 1 (namely through spray chilling), except that 37.5 g of stearyl mono(tetra)glyceride (MS-310® produced by Sakamoto Yakuhin Co., Japan; hereinafter referred to as MS-310) and 42.5 g of hydrogenated cotton seed oil were warmed and melted at 90° C. and 20 g of theophylline was put into the molten material, followed by stirring for 30 minutes to allow dispersion. There were obtained 42/60 mesh spherical fine granules.

EXAMPLE 3

By conducting spray chilling in the same manner as described in Example 2 while using:

25 g of MS-310

55 g of hydrogenated cotton seed oil

20 g of theophylline,

there were obtained 42/60 mesh spherical fine granules.

EXAMPLE 4

By carrying out spray chilling in the same manner as described in Example 2 while using:

125 g of MS-310

67.5 g of hydrogenated cotton seed oil

20 g of theophylline,

there were obtained 42/60 mesh spherical fine granules.

EXAMPLE 5

By conducting spray chilling in the same manner as described in Example 2 while using:

20 g of MS-310

40 g of hydrogenated cotton seed oil

40 g of 3,4-dihydro-2,8-diisopropyl-3-thioxo-2H-1,4-benzoxazine-4-acetic acid,

there were obtained 32/42 mesh spherical fine granules.

EXAMPLE 6

By conducting spray chilling in the same manner as described in Example 2 while using:

1 g of MS-310

109 g of hydrogenated cotton seed oil

90 g of theophylline,

there were obtained 42/60 mesh spherical fine granules.

EXAMPLE 7

By carrying out spray chilling in the same manner as described in Example 1, except that 1 g of MS-310, 45 g of lactose and 110 g of hydrogenated cotton seed oil were warmed and melted at 90° C. and 45 g of theophylline was put into the molten material, followed by stirring for 30 minutes to allow dispersion, there were obtained 42/60 mesh spherical fine granules.

EXAMPLE 8

By conducting spray chilling in the same manner as described in Example 2 while using:

1 g of MS-310

100 g of stearyl alcohol

100 g of 3,4-dihydro-2,8-diisopropyl-3-thioxo-2H-1,4-benzoxazine-4-acetic acid,

there were obtained 48/60 mesh spherical fine granules.

EXAMPLE 9

Mixed were 200 g of the fine granules as obtained in Example 8, 75 g of Avicel®, 25 g of ECG 505® (a disintegrating agent produced by Nichirin Chemical Co. of Japan) and 0.9 g of magnesium stearate, and the mixture was compressed into tablets at a pressure of 0.2 ton/cm^2 with the use of a punch of 11 mm in diameter (radius of curvature of 15 R).

EXAMPLE 10

By conducting spray chilling in the same manner as described in Example 1 after warming and melting 5 g of MS310 and 20 g of hydrogenated cotton seed oil at 90° C., charging 1 g of vinpocetine and 15 g of Eudragit L100-55 into the molten material and stirring the mixture for 30 minutes to allow dispersion, there were obtained 42/60 mesh spherical fine granules.

EXAMPLE 11

By following the same procedure as described in Example 10 while using 3 g of MS-310, 20 g of hydrogenated cotton seed oil, 1 g of vinpocetine and Eudragit L100-55, there were obtained 42/60 mesh spherical fine granules.

EXAMPLE 12

By conducting spray chilling in the same manner as described in Example 1 after warming and melting 7 g of MS310 and 21 g of hydrogenated cotton seed oil at 90° C., charging 5 g of AD-5467 and 10 g of magnesium hydroxide and stirring the mixture for 30 minutes, there were obtained 42/60 mesh spherical fine granules.

EXAMPLE 13

By following the same procedure as described in Example 12 except that 10 g of synthetic aluminum silicate in place of 10 g of magnesium hydroxide, there were obtained 42/60 mesh spherical fine granules.

EXAMPLE 14

PS-310 (91 g) was melted by heating (90° C.), idebenone (9 g) was thrown thereinto, and the mixture was melted by stirring for 30 minutes maintaining the mixture at 90° C. By the same procedure as Example 1, 60/80 mesh of fine granules were obtained.

As a comparative experiment, hardened cotton seed oil (91 g) and idebenone (9 g) were processed in the same manner as above to obtain 42/62 mesh of fine granules.

The dissolution (%; hereinafter this means weight % unless specifically defined) of the drug from these fine granules stored at 40° C. are shown in Table 1.

TABLE 1

		Dissolution (%) Hour 1	2	3	4	5	6
Fine granules made by using PS-310	Immediately after production	55.7	74.2	85.7	93.9	99.3	102.6
	After 1 month at 40° C.	60.8	73.3	82.2	88.6	92.9	96.5
	After 2 months at 40° C.	61.4	74.1	82.8	89.2	94.1	97.2
Fine granules made by using hardened cotton seed oil	Immediately after production	27.3	36.0	43.2	49.4	54.9	59.9
	After 1 month at 40° C.	33.0	44.0	53.0	61.0	68.0	74.0

From Table 1, the following facts are clarified:

The dissolution rate of idebenone from the fine granules obtained by using hardened cotton seed oil after 1 month storage at 40° C. is increased as compared with those of immediately after the production. To the contrary, the dissolution rate from the present fine granules using PS-310 shows a little change after 1 month storage and no change after 4 months storage; therefore, the release-sustaining ability of present fine granules is stable.

EXAMPLE 15

PS-310 (75 g) and MS-310 (5 g) were melted together by heating at 90° C., and then trepibutone (10 g) and magnesium oxide (30 g) were thrown thereinto and dispersed for 30 minutes maintaining the mixture at 80° C., followed by treating in the same manner as Example 1 to obtain 42/60 mesh of spherical fine granules.

The dissolution rates of the product in the mediums of I, II and pH 5 as described in J.P. 11 Ed. are shown in Table 2.

TABLE 2

	Dissolution (%) Hour 1	2	3	4	5	6
Medium I (pH 1.2)	19.4	29.4	37.1	43.8	50.0	54.7
pH 5.0	28.7	36.3	45.6	55.1	63.8	70.1
Medium II (pH 6.8)	29.5	37.6	45.5	52.9	60.7	66.8

From Table 2, it is apparent that the present fine granules exhibit almost the same rate of drug release in a wide range of pH; therefore the fine granules have stable controlled release ability.

The dissolution rates of fine granules obtained in Example 15 in medium I and II after storage for 4 months at 40° C. are shown in Table 3.

TABLE 3

	Hour					
	1	2	3	4	5	6
	Dissolution (%) in Medium I					
Immediately after production	19.4	29.4	37.1	43.8	50.0	54.7
After 4 months at 40° C.	18.9	30.0	38.1	44.2	49.2	53.7
	Dissolution (%) in Medium II					
Immediately after production	29.5	37.6	45.5	52.9	60.7	66.8
After 4 months at 40° C.	28.9	37.1	45.1	53.2	60.5	66.4

From Table 3, it is apparent that the release controlling ability of the present fine granules is extremely stable, because the dissolution rates after 4 months storage unchange as compared with those of immediately after the production.

EXAMPLE 16

PS-310 (75.2 g) and MS-310 (20.8 g) were melted together and 4 g vinpocetine and Eudragit® L100-55 (Rohm Pharma. Co., West Germany) (60 g) were put thereinto and dispersed by stirring for 30 minutes maintaining the mixture at 80° C., followed by treating in the same manner as Example 1 to obtain 42/60 mesh of spherical fine granules.

The dissolution rate of the product in mediums I and II after storage for 2 weeks and 4 months are shown in Table 4.

TABLE 4

	Dissolution (%)					
	Hour					
	1	2	3	4	5	6
Medium I (pH 1.2)	43.4	63.2	75.1	83.5	89.8	95.1
Medium II (pH 6.8)	48.9	64.7	71.5	75.4	79.1	83.6

From Table 4, it is apparent that the present fine granules are those exhibiting stable release controlling ability, because they release a drug in almost the same rate under conditions having varied pHs.

EXAMPLE 17

PS-310 (75 g) and MS-310 (21 g) were melted together by heating at 90° C., and vinpocetine (4 g) and Euragit® L100-55 (produced by Rohm Pharma. Co., West Germany) (60 g) were put thereinto and dispersed by stirring for 30 minutes maintaining the mixture at 80° C., followed by treating in the same manner as Example 1 to obtain 42/60 mesh of spherical fine granules. The dissolution rates of the product in mediums I and II after storage of 2 weeks and 4 months at 40° C. are shown in Table 5.

TABLE 5

	Hour					
	1	2	3	4	5	6
	Dissolution (%) in Medium I					
Immediately after production	36.5	56.4	69.0	77.5	84.4	89.8
After 2 weeks at 40° C.	41.6	61.4	73.1	81.5	87.9	92.6
After 4 months at 40° C.	52.5	66.5	81.0	87.0	91.6	96.4
	Dissolution (%) in Medium II					
Immediately after production	57.7	73.8	79.3	82.5	85.9	88.5
After 2 weeks at 40° C.	55.6	69.3	75.1	79.8	83.6	87.1
After 4 months at 40° C.	58.7	72.1	84.4	87.4	92.0	92.3

From Table 5, it is apparent that the present fine granules are those exhibiting stable release-controlling ability which is unchanged after two weeks in comparison to immediately after the production, and that the stability is unchanged after 4 months at 40° C.

EXAMPLE 18

PS-310 (75 g) and MS-310 (25 g) were melted together by heating at 90° C., and then AD-5467 (100 g) was put thereinto and dispersed by stirring for 30 minutes maintaining the mixture at 90° C., followed by treating in the same manner as Example 1 to obtain 42/80 mesh of fine granules.

EXAMPLE 19

PS-310 (52 g) and MS-310 (4 g) were melted together by heating at 90° C., and AD-5467 (10 g) and magnesium hydroxide (40 g) were put thereinto and dispersed by stirring for 30 minutes maintaining the mixture at 90° C., followed by treating in the same manner as Example 1 to obtain 42/60 mesh of spherical fine granules. The dissolution rates of the product after storage at 40° C. are shown in Table 6.

TABLE 6

		Dissolution (%)					
		Hour					
		1	2	3	4	5	6
Medium I	Immediately after production	54.1	69.8	77.6	91.1	96.7	99.5
	After 1 month at 40° C.	48.1	60.1	76.1	88.1	96.3	99.3
Medium II	Immediately after production	46.5	65.6	77.0	83.2	86.9	88.2
	After 1 month at 40° C.	47.3	70.5	80.7	86.1	86.4	86.4

From Table 6, it is apparent that the present fine granules are those exhibiting stable release-controlling ability which is unchanged after 1 month in comparison to those of immediately after the production.

EXAMPLE 20

PS-310 (192 g) and MS-310 (32 g) were melted together by heating at 90° C., and then AD-5467 (40 g) and magnesium hydroxide (160 g) were thrown thereinto and dispersed by stirring for 30 minutes maintaining the mixture at 90° C., followed by treating in the same manner as Example 1 to obtain 42/60 mesh of spherical fine granules.

AD-5467	40 g
PS-310	216 g
MS-310	8 g
Magnesium hydroxide	160 g

The above materials were treated in the same manner as Example 20 to obtain 60/80 mesh spherical fine granules.

The dissolution rates of the products obtained in Examples 20 and 21 in mediums I and II are shown in Table 7.

TABLE 7

		Dissolution (%)					
		Hour					
		1	2	3	4	5	6
Example 20	Medium I	66.5	89.3	97.5	100.0	100.0	100.0
	Medium II	76.7	88.5	90.5	90.3	90.6	90.8
Example 21	Medium I	36.6	50.0	58.8	65.9	71.7	76.3
	Medium II	36.8	48.4	71.8	78.5	81.8	82.5

As seen from Table 7, the present fine granules release AD-5467 at almost constant rate even under conditions having varied pHs, and granules having fast dissolution rate (Example 20) or slow dissolution rate (Example 21) independent of pH can be produced by changing the ratio of fatty acid ester of polyglycerol in present matrixes.

Fine granule preparations containing AD-5467 obtained in Examples 20 and 21, and 4 mg/ml solution of AD-5467 in aqueous 5 W/V % suspension of gum arabic as a contrast were administered to each group of four rats (SD-rat, 8 weeks aged, male), respectively.

Each material was administered to fasted animals in a dose of 10 mg/Kg (body weight) of AD-5467 and concentrations in the blood were determined (Table 8).

TABLE 8

	Concentration in blood (μg/ml)							
	Hour							
	0.25	0.5	1	1.5	2	3	5	7
Example 20	0.75	2.30	3.14	2.22	1.19	0.52	0.53	0.23
Example 21	0.16	0.73	0.88	1.12	1.23	0.79	0.57	0.69
Suspension in 5 w/v % aqueous gum arabic	5.97	2.85	1.38	0.70	0.41	0.20	0.20	0.13

Table 8 shows the following facts;

In the case of administering the aqueous suspension of gum arabic containing AD-5467, the concentration of AD-5467 in the blood reaches to the peak at 15 minutes and thereafter falls rapidly. To the contrary, present fine granules of Example 20 or 21 exhibits the peak after 1 hour or 2 hours, respectively. Therefore, present fine granules have excellent release-controlling ability.

EXAMPLE 22

Stearyl mono(deca)glyceride (produced by Sakamoto Yakuhin Co.) (92 g) was melted by heating at 90° C., and ipriflavone (18 g) was put thereinto and dispersed by stirring for 30 minutes maintaining the mixture at 90° C., followed by treating in the same manner as Example 1 to obtain 42/60 mesh of spherical fine granules.

The fine granules were administered orally to four beagles (aged 1 year, about 10 Kg) each in a dose of containing 200 mg of ipriflavone, and the concentration of 7-hydroxy-3-phenyl-4H-1-benzopyran-4-one (main metabolite of ipriflavone) in the blood was determined. The results are shown in Table 9. As the contrast, the dispersion of 200 mg of ipriflavone in 5 W/V % aqueous gum arabic suspension (hereinafter abbreviated as "suspension") was employed.

TABLE 9

	Concentration in blood (μg/ml)							
	Hour							
	0.25	0.5	1	1.5	2	3	5	7
Example 22	43.1	120.7	198	187.1	209.2	219.5	125.7	121.7
Suspension	0.1	7.2	10.3	21.9	33.0	25.0	32.1	25.6

As seen from Table 9, the absorption of ipriflavone from present fine granules obtained in Example 22 amounts to 10 times higher and sustains longer as compared with "suspension".

EXAMPLE 23

(1) PS-310 (860 g) and MS-310 (100 g) were melted together by heating at 90° C., and 90 g of phenylpropanolamine was thrown thereinto and dispersed by stirring for 30 minutes maintaining the mixture at 90° C., followed by treating in the same manner as Example 1 to obtain 30/42 mesh of spherical fine granules.

(2) The fine granules (300 g) obtained in the above (1) were loaded into a fluid-bed drier (FD-3S; Fuji Sangyo Co., Japan) and sprayed with 5 W/V % aqueous solution of hydroxypropylmethylcellulose (TC-5R; Shinetsu Chemical Co., Japan), controlling the temperature of inlet air at 45° C. and that of granules at 35° C.; thereby coated fine granules were obtained.

The dissolution rates of phenylpropanolamine in water from the fine granules obtained in Example 23 (1) and (2) are shown in Table 10.

TABLE 10

	Dissolution Hour 1	2	3	4
Example 23(1); fine granules	22.9	31.3	37.8	38.6
Example 23(2); coated fine granules	18.8	27.0	33.5	34.9

As seen from Table 10, present fine granules exhibit almost unchanged elution rate after and before coating and have stable release-controlling ability.

EXAMPLE 24

(1) PS-310 (800 g) and MS-310 (100 g) were melted together by heating at 90° C., and then caffeine (100 g) was thrown thereinto and dispersed by stirring for 30 minutes maintaining the mixture at 90° C., followed by treating in the same manner as Example 1 to obtain 42/60 mesh of spherical fine granules.

(2) The fine granules (250 g) obtained in the above (1) were loaded into a fluid-bed drier (FD-3S; Fuji Sangyo Co., Japan) and sprayed with 5 W/V % solution of hydroxypropylmethylcellulose in ethanol, controlling the inhalant air at 45° C. and the granules at 35° C.; thereby coated fine granules were obtained.

EXAMPLE 25

The fine granules (100 g) obtained in Example 24 (1), Avicel® (90 g), sodium carboxymethylcellulose (Ac-Di-Sol; FMC-Asahi Kasei Kogyo Co., Japan) (10 g) and magnesium stearate (0.6 g) were mixed and tableted with a pounder (plain) of 10 mm in diameter at 0.2 ton/cm^2 to obtain tablets.

The dissolution rates of caffeine from the fine granules obtained in Example 24 and the tablets obtained in Example 25 are shown in Table 11.

TABLE 11

	Dissolution (%) Hour 1	2	3	4	5	6
Fine granules	16.1	24.5	33.4	38.3	43.8	46.5
Tablets from coated fine granules	17.2	27.8	36.7	45.5	48.9	51.4

As seen from Table 11, caffeine release from the tablets produced by tabletting coated fine granules (Example 25) occurs in the same rate as from the coated fine granules not being compressed to tablets (Example 24), and the both preparations exhibit stable release-controlling ability.

EXAMPLE 26

PS-310 (64 g) and MS-310 (16 g) were melted together by heating at 90° C., and 20 g of delapril was thrown thereinto and dispersed by stirring for 30 minutes maintaining the mixture at 70° C., followed by treating in the same manner as Example 1 to obtain 60/80 mesh of spherical fine granules. The dissolution rates of delapril from the fine granules are shown in Table 13.

TABLE 13

	Dissolution (%) Hour 1	2	3	4	5	6
60/80 mesh fine granules	48.3	74.1	85.5	90.1	92.3	93.0

The fine granules obtained in the above procedure were administered to a rat under fast overnight in a dose of 20 mg/Kg as delapril and the concentration of (N-[N-[(S)-1-carboxy-3-phenylpropyl]-L-alanyl]-N-indan-2-yl) glycine (metabolite of derapuryl hydrochloride) in the blood was determined and shown in Table 14. As a contrast, a solution of depnrayl hydrochloride (4 mg/ml) in 5 W/V % aqueous suspension of gum arabic was used.

TABLE 14

	Concentration in blood (μg/ml) Hour 0.25	0.5	1	1.5	2	3	5	7
60/80 mesh fine granules	0.881	0.816	0.785	0.647	1.07	0.387	0.115	0.052
Suspension of delapril hydrochloride in 5 w/v % aqueous gum arabic	5.46	4.63	0.875	0.427	0.221	0.200	0.090	0.007

As seen from Table 14, in the case of administering the solution of delapril hydrochloride, rapid disappearance of concentration in the blood is observed, but the present fine granules exhibit sustained concentration in the blood corresponding to the dissolution rate. See Table 13 for the dissolution rates of the 60/80 mesh fine granules.

EXAMPLE 27

MS-310 (8 g), PS-310 (32 g) and stearyl tri(mono)glyceride (TS-310; produced by Sakamoto Yakuhin Co., Japan) (40 g) were melted together by heating and the temperature of the mixture was adjusted to 70° C., and then 20 g of delapril was thrown thereinto and dispersed by stirring for 30 minutes, followed by treating in the same manner as Example 1 to obtain 42/60 mesh of fine granules.

EXAMPLE 28

The fine granules (250 g) obtained in Example 27 were loaded into a fluid-bed drier (FD-35; Fuji Sangyo Co., Japan) and sprayed with 5 W/W % solution of hydroxypropylcellulose in ethanol for coating, controlling the inhalant air at 45° C. and granules at 35° C.; thereby coated fine granules were obtained.

EXAMPLE 29

The coated fine granules (100 g) obtained in Example 28, Avicel® (90 g), sodium carboxymethylcellulose (Ac-Di-Sol; FMC-Asahi Kasei Kogyo Co., Japan) (10 g) and magnesium stearate (0.6 g) were mixed and tableted with a punch (plain) of 10 mm in diameter at the pressure of 0.2 ton/cm^2 to obtain tablets.

The dissolution rates of derapuryl hydrochloride from the fine granules, coated granules or tablets of Examples 27, 28 and 29 are shown in Table 15.

TABLE 15

	Dissolution (%)					
	Hour					
	1	2	3	4	5	6
Example 27	56.9	83.3	89.8	89.9	89.2	:9&.6
Example 28	51.5	78.4	89.2	92.6	93.1	92.5
Example 29	62.9	85.9	89.5	91.0	91.9	92.5

As seen from Table 15, the release of delapril hydrochloride from the present coated fine granules (Example 28) or tablets obtained by tabletting the coated fine granules (Example 29) is unchanged as compared with the fine granules before coating (Example 27), and all of them exhibit stable and sustained dissolution.

EXAMPLE 30

PS-310 (65.6 g) and MS-310 (9.4 g) were melted together at 90° C., and delapril hydrochloride (25 g) was thrown thereinto and dispersed by stirring for 30 minutes maintaining the mixture at 70° C., followed by treating in the same manner as Example 1 to obtain 42/60 mesh of spherical fine granules.

The release of delapril hydrochloride from the fine granules when they were stored at 40° C. is shown in Table 16.

TABLE 16

	Dissolution (%)					
	Hour					
	1	2	3	4	5	6
Immediately after production	38.4	57.1	74.3	83.2	85.7	86.8
After 10 days at 40° C.	38.9	58.8	73.2	80.7	83.8	84.1
After 3.5 months at 40° C.	35.8	53.2	66.2	74.5	79.0	81.7

As seen form Table 16, present fine granules have excellent release-controlling ability even after a long period of storage, which proves that they are extremely stable controlled release preparation.

EXAMPLE 31

The fine granules obtained in Example 17 were filled into capsule No. 1 of J.P. 11 Ed. to obtain a capsule preparation.

EXAMPLE 32

The fine granules obtained in Example 18 were tableted with a punch (plain) of 6 mm in diameter at the pressure of 0.1 ton/cm^2 to obtain tablets.

EXAMPLE 33

In the same manner as Example 24 (1) with a 900 rpm rotation number of the disk, employing PS-310 (800 g), MS-310 (100 g) and caffeine (100 g), 12/48 mesh of granules were obtained.

We claim:

1. Fine granules or granules which comprise a pharmaceutically active ingredient dispersed into a matrix which is solid at ambient temperature and and contains a fatty acid ester of a polyglycerol, the ester being present throughout the fine granules or granules; wherein said fine granules are composed of not less than 75 weight % of particles of 500 to 10 μm, not more than 5 weight % of particles of not less than 500 μm, and not more than 10 weight % of particles of not more than 10 μm; and wherein said granules are composed of not less than 90 weight % of particles of 1410 to 500 μm and not more than 5 weight % of particles of not more than 177 μm.

2. Fine granules or granules according to claim 1, wherein microcrystalline wax is contained in the matrix.

3. Fine granules or granules according to claim 2, wherein the fine granules or granules are coated with a coating agent.

4. Fine granules or granules according to claim 1, wherein the fine granules or granules are coated with a coating agent.

5. Fine granules or granules according to claim 1, wherein the amount of the fatty acid ester of polyglycerol in the matrix is about 0.0001 to 50 times the weight of the pharmaceutically active ingredient.

6. A capsule comprising fine granules or granules which comprise a pharmaceutically active ingredient dispersed into a matrix which is solid at ambient temperatures and contains a fatty acid ester of a polyglycerol, the ester being present throughout the fine granules or granules, said fine granules being composed of not less than 75 weight % of particles of 500 to 10 μm, not more than 5 weight % of particles of not less than 500 μm and not more than 10 weight % of particles of not more than 10 μm and said granules being composed of not less than 90 weight % of particles of 1410 to 500 μm and not more than 5 weight % of particles of not more than 177 μm.

7. A capsule comprising fine granules or granules which comprise a pharmaceutically active ingredient dispersed into a matrix which is solid at ambient temperatures and contains a fatty acid ester of a polyglycerol, the ester being present throughout the fine granules or granules, said fine granules being composed of not less than 75 weight % of particles of 50 to 10 μm, not more than 5 weight % of particles of not less than 500 μm and not more than 10 weight % of particles of not more than 10 μm and said granules being composed of not less than 90 weight % of particles of 1410 to 500 μm and not more than 5 weight % of particles of not more than 177 μm, wherein the fine granules or granules are coated with a coating agent.

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